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Pathology

EXPERIMENTAL PATHOLOGY

1255. **Morphological Characteristics of the Vaccinal Process in Brucellosis.** (Морфологическая характеристиоа вакцинного процесса при бруцеллезе (Экспериментальное исследование))
V. F. SOLOMINA. *Архив Патологии* [*Arh. Patol.*] **20**, 30–35, No. 3, 1958. 1 fig., 5 refs.

The author describes a histological study of the effects of experimental inoculation with the Dorofeiev–Chalisov live vaccine prepared from *Brucella melitensis* on 204 guinea-pigs. During the first 24 hours after inoculation a general " activation of the reticulo-endothelial elements in the tissues of internal organs " was observed, the reticulo-endothelial cells swelling up and some of them " losing their syncytial connexions and being transformed into free macrophages ". Moreover, soon after vaccination small inflammatory foci appeared in the liver, spleen, and lymph nodes.

As early as one hour after inoculation with this live vaccine a positive culture could be obtained from the inoculated animal's organs, showing a very rapid spread of the organisms in the body. About 5 days after inoculation the acute reaction subsided and foci of reticuloendothelial-cell proliferation made their appearance. Proliferative reaction reached its peak by the end of the 2nd month and subsided 4 months after inoculation. Positive cultures were obtained from the animals' organs as late as 30 days after inoculation. Wright's reaction became positive in not less than 15 days, and the skin test " much later ". The vaccine was found to be effective in protecting guinea-pigs from brucellosis, subcutaneous inoculation proving effective in 70% of the animals and intradermal inoculation in over 80%.

A. Swan

1256. **Absorption of Blood from the Pleural Cavity under the Conditions of Experimentally Induced Haemothorax and Haemopneumothorax.** (Всасывание крови из плевральной полости в условиях экспериментального гемоторакса и гемопневмоторакса)
S. S. LAGUČEV. *Архив Патологии* [*Arh. Patol.*] **20**, 43–54, No. 3, 1958. 8 figs., 30 refs.

Haemothorax was induced experimentally in 5 dogs, 16 cats, and 11 rabbits, and haemopneumothorax in 18 cats and 10 rabbits. To induce the former blood from the animal's jugular vein was immediately introduced into its right pleural cavity, the amount of blood used being 0·5 ml. per kg. of the animal's body weight. In inducing the haemopneumothorax 100 to 150 ml. of air was introduced into the same pleural cavity after the blood. It was found that absorption of blood from the pleural cavity of animals takes place much more rapidly than in man; thus it was complete within 48 hours in cats, was still more rapid in dogs, but was somewhat slower in rabbits (4 to 5 days).

In the first two species autogenous blood produced no inflammatory changes in the pleura, whereas in rabbits there was an inflammatory reaction, with consequent easily observable stagnation of lymph flow and accumulation of erythrocytes absorbed from the pleural cavity in the lymph vessels. The author suggests that the cause of retarded blood absorption in rabbits, as well as in man, is the inflammatory response of the pleura to the contact with autogenous blood. The additional presence of air in the pleural cavity produced marked inflammatory changes in the pleura in all three species and consequently led to a reduction in the rate of blood absorption. This delay in absorption, it is argued, could not be due to an increase in intrapleural pressure, for this increase is of very short duration. Haemolysis was absent in the majority of cases, the erythrocytes being absorbed intact via the lymphatics. In further observations on rabbits with bilateral haemothorax, but with additional air on one side only, retardation of blood absorption was observed on both sides, although not to the same extent. In the author's opinion this points to a reflex mechanism of retardation of blood absorption after the induction of pneumothorax. *A. Swan*

1257. **A New Method of Inducing Prolonged Hypertension of Neurogenic Origin in Dogs.** (О новом методе получения стойкой гипертонии нейрогенной природы у собак)
V. A. BUKOV, L. A. BYKOV, V. A. VALUK, R. A. VARTBARONOV, E. F. ŽILIS, V. M. KONDRAKOV, V. A. KUZMIN, G. I. SYČEV, N. I. FROLOV, A. S. FOKIN, and A. N. HARINSKIJ. *Архив Патологии* [*Arh. Patol.*] **20**, 21–27, No. 5, 1958. 5 figs., 21 refs.

Hypertension lasting 5 months was induced in 6 dogs by intermittent electrical stimulation of the vagus nerves or by stimulation of the gastric receptors with cold water introduced through a gastric fistula. Both methods of stimulation were applied on the background of oxygen deprivation achieved by making the dogs breathe from a small closed space (a 15-litre flask connected with a mask). Oxygen deprivation " exhausted the functional capacity of the vagal nuclear system " and thus, it is claimed, made it more susceptible. Stimulation of vagal receptors, either electrical or thermal, under

these conditions tended to induce the state of stable "post-liminal" inhibition in the vagal and related centres, leading to hypertension. Three stimulations at intervals of 5 minutes were administered during each of the experiments, which were performed 2 or 3 times a week, the total number of experiments on 6 dogs over 2 years being over 300. *A. Swan*

1258. **The Role of Aortotoxic Serum in the Localization of Pathological Processes.** (Роль аортотоксической сыворотки в локализации патологического процесса) N. A. Levkova. *Архив Патологии* [*Arh. Patol.*] **20**, 39–45, No. 5, 1958. 4 figs., 7 refs.

At the Pirogov Second State Medical Institute, Moscow, an antiserum to the aortic tissue of the rabbit was produced in geese and then used for the immunization of healthy rabbits by means of repeated small (1 to 2 ml.) intravenous injections spread over periods of 15 to 60 days. At the end of this course a "resolving" dose of the same aortotoxic serum was then given. In 2 of the rabbits (out of 5) which survived the immunization process and the "resolving" injection of aortotoxic serum non-bacterial endocarditis, "intracapillary" nephritis and, in one of them, focal necrosis of the aortic wall were demonstrated.

In another group of 15 rabbits the resolving injection was supplemented by a living culture of *Streptococcus viridans*. In 9 animals in this group ulcerative endocarditis was found at necropsy, and in others "diffuse productive extracapillary glomerulonephritis". A similar picture of allergic vasculitis was demonstrated in 10 animals in which the preliminary immunization was carried out with normal goose serum, and the resolving dose consisted of 3 ml. of the aortotoxic serum plus *Strep. viridans*. The author states that if the preliminary immunization is performed with serum from an animal species different from that in which the aortotoxic serum is produced (for example, horse serum) the "resolving" inoculation of aortotoxic goose serum and *Strep. viridans* is followed by a stormy septic process due, according to the author, to "extinguishing of the immune properties of the organism". [These experiments appear to be of some interest inasmuch as in a proportion of positive cases there was focal ulceration of the aorta itself.] *A. Swan*

1259. **Experimental Studies of the *in vivo* Relationships of the Properdin System to Resistance to Infection**
O. A. Ross. *American Journal of Pathology* [*Amer. J. Path.*] **34**, 471–485, May–June, 1958. 15 refs.

The properdin system in human serum was originally described by Pillemer *et al.* (*Science*, 1955, **120**, 279). In this study of the relationship between serum properdin levels and resistance to infection, reported from Western Reserve University School of Medicine, Cleveland, Ohio, groups of mice were injected intraperitoneally with *Escherichia coli* in doses ranging from $3{\cdot}4\times10^4$ to $3{\cdot}4\times10^9$. After the highest dosage the serum properdin titre fell to approximately 10% of the pre-injection levels within one hour and all the mice died. Following the lower doses there was a transient fall in the serum properdin level, ranging from 25 to 50%, which was detectable 24 hours after inoculation, while the death rate was only 15%. The serum properdin level returned to normal within 72 hours.

The intravenous administration of zymosan (the insoluble residue of ordinary baker's yeast) to mice in doses of 5 and 25 mg. per kg. body weight resulted in an immediate reduction of the serum properdin titre to 50% of its original value for the first 4 hours, but after 72 hours the titre had risen to 200% and remained at this level for 10 days. With doses of 125 mg. per kg., however, the titre immediately fell to 16% of the original level and had recovered to only 75% of that level after 10 days. Similar results were obtained in rats. After serum properdin levels had returned to normal, foci of intracellular particles positive to periodic-acid–Schiff staining could be demonstrated for up to 3 months in mouse tissues, suggesting that there was retention of zymosan. In further groups of mice inoculated intraperitoneally with *Klebsiella pneumoniae* (15 or 75 organisms) from one to 12 weeks after intravenous administration of zymosan in doses of 25 or 125 mg. per kg. a considerably increased survival rate was observed in all groups, amounting to 100% in the most recently protected.

The intravenous injection of partially purified human properdin prepared by the zymosan-elution procedure into mice in doses of 20 or 50 units raised the serum properdin level 2- to 4-fold for 24 hours, and in doses of 60 units injected 4 hours or 15 minutes before or 2 hours after inoculation with lethal doses of *Klebs. pneumoniae* resulted in appreciably increased survival rates. Increased survival rates were also observed following injection of heat-inactivated human properdin, even though assay *in vitro* showed its activity to be less than one unit of properdin per ml. Purified human properdin derived from serum by chemical methods not requiring the use of zymosan adsorption was also as effective as zymosan properdin in protecting mice from infection.

(These observations are presented as preliminary findings only.) *A. Ackroyd*

CHEMICAL PATHOLOGY

1260. **Serum Macroglobulin Levels in Relation to Age, Sex, and Disease**
E. Eriksen. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **51**, 521–529, April, 1958. 4 figs., 9 refs.

The author, working at the University of Washington, Seattle, has determined the macroglobulin ($S>15$) levels in 151 specimens of serum from 28 healthy and 123 diseased individuals of both sexes and all ages; patients with Waldenström's macroglobulinaemia or apparently related conditions were excluded from the study, while a special effort was made to include those with multiple myeloma (17). The series included 10 patients with asthma or other allergic manifestation whose serum protein patterns were being studied electrophoretically. The sera were subjected to ultracentrifugal analysis at

59,780 r.p.m. and a bar angle of 60 degrees. Whole serum was diluted with 5 to 7 volumes of M/10 NaCl; serum fractions other than those obtained electrophoretically were dialysed against M/10 NaCl before analysis, while electrophoretically separated fractions were analysed as obtained in barbitone buffer. Moving-boundary electrophoretic analyses were carried out at accurately determined serum dilutions (final dilution factor $\geqq 5$) in barbitone buffer, ionic strength 0·1, *p*H $8{\cdot}55 \pm 0{\cdot}05$. The total protein values were calculated by use of a factor relating total electrophoretic area to the dry weight of solids retained by a dialysing membrane.

The mean value for healthy and many diseased adults was in the region of 0·3 g. per 100 ml., women having a slightly higher level than men. The mean value for infants and children, excluding obvious pathologically raised values, was approximately 0·4 g. per 100 ml., an increase which was shown to be statistically significant ($P<0{\cdot}01$). Patients with the nephrotic syndrome had consistently high values (1·1 g. per 100 ml.), whereas low values (0·15 g. per 100 ml.) were found in patients with multiple myeloma. Widely different values were found in various other conditions, but the heterogeneity of the case-material and the frequent lack of definite diagnoses made interpretation difficult. A study of the electrophoretic distribution of macroglobulin showed that both the α_2- globulin and γ-globulin fractions were implicated as sites of significant variation in the macroglobulin level of the cases studied. *Victor M. Rosenoer*

1261. **Faecal Occult Blood Tests without Dietary Restrictions**

R. L. SMITH. *British Medical Journal* [*Brit. med. J.*] **1**, 1336–1338, June 7, 1958. 3 refs.

Because of difficulty in obtaining benzidine a number of tests for the detection of occult blood in faeces which do not involve the use of this drug or any dietary restriction were studied at Chase Farm Hospital, Enfield, Middlesex. Three faecal specimens from each of 45 patients aged 16 to 85 years who were receiving a normal hospital diet (excluding liver) and had no signs or symptoms of haemorrhage into the gastro-intestinal tract were examined by the *ortho*tolidine method of Kohn and O'Kelly (*J. clin. Path.*, 1955, **8**, 249; *Abstr. Wld Med.*, 1956, **19**, 180) at five sensitivity levels. Of a stock solution of 4% *ortho*tolidine five dilutions with 50% v/v acetic acid were prepared—namely, 33%, 20%, 10%, 5%, and 2%. Specimens of faeces from a healthy subject were tested after blood had been added (3 to 2,700 mg. of haemoglobin per 100 g. of faeces) by: (1) the *ortho*tolidine method at five sensitivity levels; (2) the "occultest" tablet test; (3) the "hematest" tablet test [the composition of the tablets is not given]; and (4) Gregersen's slide test, the results of the tests being compared.

With the 5% dilution of the stock *ortho*tolidine solution there was "a reasonable compromise" between a high incidence of false positive results and a low sensitivity, and this dilution is therefore recommended for testing faeces from patients on a normal diet provided foods containing a large amount of blood—for example, liver—have been excluded. It is stated that the sensitivity of the modified test with a 5% dilution is much less than that of the standard *ortho*tolidine test in which 33% dilution is used, is slightly less than that of the Gregersen slide test, and is similar to that of the tablet tests. Strongly positive results are significant, but false positive and weakly positive results are obtained in up to 10% of cases. The occultest tablet test is recommended for ward use. *J. E. Page*

HAEMATOLOGY

1262. **Immunological Studies of Disseminated Lupus Erythematosus.** (Études immunologiques sur le lupus érythémateux disséminé)

M. SELIGMANN. *Revue française d'études cliniques et biologiques* [*Rev. franç. Ét. clin. biol.*] **3**, 558–584, June, 1958. 6 figs., bibliography.

The results are reported of an extensive immunological study of 40 samples of serum from 19 cases of disseminated lupus erythematosus carried out at the Institut Pasteur and the Hôpital Saint-Louis, Paris. The methods used are described.

The author was able to obtain specific precipitation and complement-fixation reactions with a significant proportion (29) of these sera using leucocyte, platelet, and human, animal, and bacterial deoxyribonucleic acid (D.N.A.) preparations which had been subjected to ultrasonic disintegration in order to reduce the molecular size so that gel diffusion could take place. He concludes that the responsible serum factors are antibody in nature, since immuno-electrophoretic, precipitation, and complement-fixation studies showed the presence in most sera of three different antibodies singly or in combination: (1) to leucocyte extracts, (2) to D.N.A., and (3) post-transfusion. Extraction of the antibodies from the specific precipitates showed that they were γ globulins and also that the extracted antibody was capable of inducing the L.E.-cell phenomenon. More than half the sera showed precipitation and fixation of complement with platelet extracts, although the results of these two tests were not exactly comparable. The sera were still able to react with D.N.A. and leucocyte extracts after absorption with platelets. No correlation could be established between the platelet count and the presence of antibodies. The author suggests the possibility of an auto-antibody to account for these antibodies.

A significant proportion of the sera showed an increased titre of leucocyte antigens on precipitation with antileucocyte sera, which is attributed to increased leucocyte breakdown. The author then discusses the significance of these antibodies in relation to the L.E.-cell phenomenon and the pathogenesis of lupus erythematosus, postulating as a possible antigenic stimulus bacterial D.N.A. acting as a hapten. Since the absorption of D.N.A. alone does not remove the ability of sera to form L.E. cells he suggests that a variety of antibodies to other nucleoprotein components may exist. The paper includes an extensive bibliography containing over 100 references. *D. M. Weir*

1263. **Starch Block Electrophoretic Studies of Human Hemoglobin Solutions. I. Technic and Results in the Normal Adult**
M. S. MASRI, A. M. JOSEPHSON, and K. SINGER. *Blood* [*Blood*] **13**, 533–542, June, 1958. 4 figs., 32 refs.

The work here reported from the Medical Research Institute of the Michael Reese Hospital, Chicago, (which was initiated by the late Dr. Karl Singer and was nearly completed before his death) consists in a study of normal adult haemoglobin by means of zone electrophoresis on starch granules. The preparation of the starch block and of the buffer system are described in considerable detail. In the typical electrophoretic pattern 4 components could be observed. The bulk of the haemoglobin, amounting to more than 90%, was in the major band, referred to as A_1. Two bands moving more slowly than A_1 at alkaline *p*H were designated A_2 and A_4; the mobility of A_4 was slower than, and that of A_2 identical with, that of haemoglobin E. The band designated A_3 moved faster than A_1, but did not separate from it completely. (It is of technical interest that there seemed to be a better separation after the same starch sample had been re-used as the supportive medium for electrophoresis several times than when it was used for the first time.)

The average relative concentration of the A_2 component in blood from 200 normal subjects was 2·55% (range 1·2 to 3·5%); that of the A_4 component was less than 1%; and that of the A_3 component (which could not be determined accurately owing to incomplete separation from the A_1 band) about 2 to 5%.

In haemolysates of normal blood prepared by the usual methods two non-haemoglobin components were also distinguished, one moving just behind A_4 and one moving faster than A_3. It is suggested that the former may represent a water-soluble stroma fraction and the latter the "X" fraction of Derrien or an enzyme such as methaemoglobin reductase (Lonn and Motulsky, *Clin. Res. Proc.*, 1957, **5**, 157). *H. Lehmann*

1264. **Starch Block Electrophoretic Studies of Human Hemoglobin Solutions. II. Results in Cord Blood, Thalassemia and Other Hematologic Disorders: Comparison with Tiselius Electrophoresis**
A. M. JOSEPHSON, M. S. MASRI, L. SINGER, D. DWORKIN, and K. SINGER. *Blood* [*Blood*] **13**, 543–551, June, 1958. 1 fig., 21 refs.

In a further report on the study of haemoglobin by means of starch block electrophoresis [see Abstract 1263] the authors describe their findings in specimens of cord blood and of blood from patients with various types of anaemia and haemoglobinopathy. The A_2 fraction of haemoglobin was found to be virtually absent from cord blood, but its relative concentration was increased in the blood of all of 34 patients with thalassaemia and also in that of 5 out of 9 patients with pernicious anaemia. The relative concentration of haemoglobin A_2 tended to be low in 30 cases of iron-deficiency anaemia and to return to normal after successful iron therapy.

To determine the relation between the A_2 component and the small unidentified component previously noted by Singer *et al.* (*Blood*, 1954, **9**, 1032; *Abstr. Wld Med.*, 1955, **17**, 386) in haemolysates of thalassaemic blood examined in the standard Tiselius apparatus a quantitative comparison of these two components in blood from patients with thalassaemia and other haematological disorders was carried out. Haemolysates in which the A_2 component on starch electrophoresis was within the normal range consistently gave a pattern of pure haemoglobin A in the Tiselius apparatus. *H. Lehmann*

MORBID ANATOMY AND CYTOLOGY

1265. **Rubella during Pregnancy. 2. Studies on the Dental Development in the Foetus.** [In English]
G. BERGMAN, R. LUNDSTRÖM, and L. LYSELL. *Acta pathologica et microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **43**, 41–46, 1958. 3 figs., 8 refs.

In a previous report Lundström (*Acta path. microbiol. scand.*, 1957, **41**, 449; *Abstr. Wld Med.*, 1958, **24**, 9) described the macroscopic appearances in over 60 foetuses obtained by therapeutic abortion during an epidemic of rubella in Sweden in 1951. In this second study from Karolinska Institutet, Stockholm, the authors have investigated the dental development in 29 of these foetuses. The jaws from both sides were taken at random in 6 cases and compared with 3 control cases, while in a further 23 cases a histological study of the dental primordia was made in the jaws from one side only. In only one instance was an abnormality noted, in one of the cases in which the whole jaw was examined. This consisted in premature eruption of the upper incisors, a feature which was thought to be real and not due to an artefact caused during abortion or in the process of fixation. *J. B. Wilson*

1266. **Squamous Metaplasia of the Respiratory Tract Epithelium. An Autopsy Study of 214 Cases. 2. Relation to Tobacco Smoking, Occupation and Residence.** [In English]
K. SANDERUD. *Acta pathologica et microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **43**, 47–61, 1958. 7 refs.

A recent paper by the author (*Acta path. microbiol. scand.*, 1958, **42**, 247; *Abstr. Wld Med.*, 1958, **24**, 163) reported the incidence, with age and sex distribution, of squamous metaplasia in 214 subjects coming to necropsy. In this further communication from the Gade Institute, University of Bergen, he discusses further aspects of this lesion in relation to smoking habits, occupation, and place of residence.

Squamous epithelial metaplasia of the respiratory tract was found in 80% of male smokers, but in only 54% of male non-smokers, and its extent varied with the duration and type of smoking and the amount of tobacco consumed; thus the metaplasia was of Grade III in 53% of cigarette smokers, but in only 30% of pipe smokers and 18% of non-smokers. The relationship between these changes and occupation (classed as "open-air", "clerical or professional", and "dusty") was less marked, but still definite, the figures for incidence of metaplasia being 51, 69, and 79% respectively for the

three types of occupation. Similarly, residence in a "dusty" (that is, urban as opposed to rural) area gave a slightly increased incidence of metaplasia. Farmers and seamen were considered separately. The paper contains a number of useful tables showing the breakdown of these over-all figures for men and women, light, moderate, and heavy smokers, non-smokers, and different age groups. *J. B. Wilson*

1267. **A Pathological Study of Emphysema of the Lungs with Chronic Bronchitis**
B. E. HEARD. *Thorax* [*Thorax*] **13**, 136–149, June, 1958. 15 figs., 20 refs.

At the Postgraduate Medical School of London the lungs obtained at necropsy from a number of patients with clinical evidence of chronic bronchitis were examined for the presence of emphysema, a simple method for prolonged, even distension of the lungs with formalin at a continuous pressure of 25 cm. being employed. Impregnation of slices of the fixed material with barium sulphate removed the translucency, thereby permitting reliable and detailed study of lung pattern in emphysema. Additional information was obtained in some instances by the preliminary injection of pulmonary arteries with a barium–gelatin mixture. Study of the lungs in this small series of cases of chronic bronchitis revealed widespread centrilobular emphysema, whereas in the lungs of patients without bronchitis there was, at most, only very mild emphysema in a few scattered lobules.

On the basis of the findings the author suggests that there are two types of emphysema, diffuse and centrilobular, each of which may be widespread or localized. He also refers to a "paraseptal" variety, and states that mixed types may occur. *A. Wynn Williams*

1268. **Occult Tuberculous Endobronchitis in Surgically Resected Lung Specimens**
J. R. THOMPSON and G. KENT. *American Review of Tuberculosis and Pulmonary Diseases* [*Amer. Rev. Tuberc.*] 77, 931–939, June, 1958. 5 figs., 8 refs.

The incidence of tuberculous endobronchitis in pulmonary tissue obtained by resection in 344 consecutive cases was studied at the City of Chicago Municipal Tuberculosis Sanitarium. Histological evidence of tuberculous endobronchitis was found in 44 (12·8%) of the cases (pneumonectomy in 11, lobectomy in 26, and segmentectomy in 7). The majority of the lesions were situated within or adjacent to sero-mucinous lymph nodes. Cavitation was present in 40 (90·9%) of the 44 cases, compared with 103 (34·3%) of the 300 with non-tuberculous endobronchitis. Tuberculous lymphadenitis was present in 6 (14·4%) of the cases in the former group and in 6 (2%) of the cases in the latter group. Tubercle bacilli were cultured from material aspirated from the bronchi in 25 out of 39 cases of tuberculous endobronchitis compared with 13 out of 199 cases of non-tuberculous endobronchitis.

The authors consider that in view of the high incidence of associated cavitation and positive cultures endobronchial disease is, in the majority of instances, the result of surface implantation of bacilli, possibly through the glandular ducts. However, the finding of lymph-node involvement in 6 (14·4%) of cases suggests that lymphatic extension may be a cause of tuberculous endobronchitis. *H. Caplan*

1269. **"Rheumatic" Pneumonia with Pulmonary Hyaline Membrane.** (Über die sog. rheumatische Pneumonie mit pulmonalen hyalinen Membranen)
H. LAPP and G. MALECH. *Frankfurter Zeitschrift für Pathologie* [*Frankfurt. Z. Path.*] **69**, 194–205, 1958. 3 figs., 25 refs.

With reference to 3 cases examined post mortem at the Pathological Institute of the Justus Liebig University, Giessen, the authors discuss the morbid anatomy of the pneumonic condition occasionally associated with rheumatic carditis. Macroscopically, the lungs show ill-defined areas of consolidation, not confined to any one lobe; the consistency of these areas is less firm than in the hepatization of lobar pneumonia and their colour depends on the amount of cardiac back-pressure which has been present. Histologically, there is a non-suppurative, partly haemorrhagic pneumonia, with hyaline membranes lining the alveoli and terminal bronchioles. The thickness of the membranes varies from a few microns upwards; they are sharply demarcated from the alveolar wall, and occasionally a connexion between the membranes in adjacent alveoli through the alveolar pores may be noted. Irregular coarse layering of the hyaline material can sometimes be seen, and it may be acellular or contain round cells of varying size. Some alveoli contain spherical hyaline masses (Masson bodies) enclosing alveolar epithelial cells and showing signs of organization by ingrowing fibroblasts. The hyaline material can be distinguished from oedema fluid and from fibrin by its staining reactions; it gives a positive periodic-acid–Schiff reaction. No neutral fat is demonstrable. There is also proliferation of the pericapillary endothelium to form large cells, usually mononuclear but occasionally multinuclear, with a basophil cytoplasm. These cells may be found in the alveolar lumen and in the Masson bodies.

The authors consider that there is a fundamental difference between the pulmonary hyaline membranes found in uraemia, plague, and poisoning with phosgene and other substances in man and in experimental oxygen and carbon dioxide poisoning in animals, in which the hyaline material is derived from necrotic alveolar cells, and those found in interstitial plasma-cell pneumonia of the newborn, poliomyelitis, pneumonia of premature infants, and rheumatic pneumonia, in which it lies on a healthy alveolar wall. They point out that although the latter group contains conditions of widely differing aetiology the hyaline material in all of them is derived from the blood. In the rheumatic process there is a disturbance of the ground substance of connective tissue which is reflected in an increase in the serum glucoprotein and globulin content. This dysproteinaemia may account for the unusual appearance of the inflammatory exudate in rheumatic pneumonia, and a similar mechanism may operate in the other conditions mentioned.
F. Hillman

1270. **Pulmonary Arteriosclerosis and Thromboembolism in Chronic Pulmonary Emphysema**
J. A. KERNEN, R. M. O'NEAL, and D. L. EDWARDS. *A.M.A. Archives of Pathology* [*A.M.A. Arch. Path.*] **65**, 471–478, May, 1958. 4 figs., 23 refs.

At the Universities of Indiana, Indianapolis, and Washington, St. Louis, the authors have investigated the incidence and degree of pulmonary arteriosclerosis and thrombo-embolism as noted in the post-mortem records of 125 patients dying with chronic diffuse pulmonary emphysema, and for comparison those of 54 patients without significant cardiac or pulmonary disease.

Of the 125 cases of emphysema, 45 (36%) showed right ventricular hypertrophy (a thickness of 6 mm. or more), which was taken as presumptive evidence that pulmonary hypertension had been present; in contrast, in none of the control patients was there evidence of right ventricular hypertrophy. On the other hand the incidence and degree of pulmonary arteriosclerosis (based on examination of small muscular pulmonary arteries) were not significantly greater among the patients with emphysema than in the control group; nor was there a significant correlation between such arteriosclerosis, when present, and right ventricular hypertrophy. However, a significant correlation between advanced pulmonary arteriosclerosis and thrombo-embolic phenomena was established.

The pathogenesis of pulmonary hypertension is briefly discussed, and although its aetiology is as yet undetermined, the authors conclude that it is not responsible, as was previously thought, for pulmonary arteriosclerosis.

G. J. Cunningham

1271. **The Pathologic Physiology of Microscopic Pulmonary Vascular Shunts**
F. R. HUFNER and C. A. MCNICOL. *A.M.A. Archives of Pathology* [*A.M.A. Arch. Path.*] **65**, 554–560, May, 1958. 10 figs., 29 refs.

The authors describe 3 cases in infants seen at Huntington Hospital, New York, of a rare condition consisting in endoarterial obliterative vascular lesions in the lungs, resulting in cardio-respiratory failure and death. The patients, 3 girls aged 11, 13, and 22 months respectively, all died within the first 2 years of life and presented similar lesions which were confined to the pulmonary vessels. In all cases the disease affected the small muscular arteries (but not the larger), those of 1 to 2 mm. diameter giving off branches which showed extreme endothelial proliferation and finally obliteration. The involved arteries were peribronchial in situation, and the lesion produced changes which are described as "glomoid" and "angiomatous". There was no inflammatory component.

Discussing this unusual condition as seen in these and other cases reported in the literature the authors note that in the majority it was accompanied by a single congenital cardiac defect. They suggest that the vascular lesions probably represent "shunts" between muscular branches of the pulmonary artery and smaller, non-muscular, vascular channels. In the absence of any evidence of an inflammatory or post-thrombotic condition the aetiology of the obliterative changes observed in the vessels is not apparent. In all 3 cases there was pronounced hypertrophy of the right heart, and the authors conclude that the terminal cardiac failure is brought about by obliterative lesions interfering with the action of these pulmonary "shunts". *G. J. Cunningham*

1272. **Bronchogenic Cysts and the Theory of Intralobar Sequestration: New Embryologic Data**
E. A. BOYDEN. *Journal of Thoracic Surgery* [*J. thorac. Surg.*] **35**, 604–616, May, 1958. 9 figs., 25 refs.

Solitary bronchogenic cysts have been regarded as congenital in nature. Pryce and his associates reported (*J. Path. Bact.*, 1946, **58**, 457; *Abstr. Wld Med.*, 1947, **1**, 407; also *Brit. J. Surg.*, 1947, **35**, 18) the frequent coincidental occurrence of a systemic or accessory pulmonary artery with this abnormality. It was therefore suggested that the two conditions are related and that the mechanism is one of traction by the systemic aberrant artery on the capillary network of the developing bronchial tree, the cysts representing "sequestered" masses of pulmonary tissue within the lung. With this thesis, however, the present author, writing from the University of Washington, Seattle, does not agree. He points out that the two anomalies do not always occur together and adduces embryological evidence in support of his view.

Examination of serial sections of part of the collection of early embryos at the Carnegie Laboratory of Embryology, Baltimore, resulted in the finding of bilateral bronchogenic cysts in a 31-mm. human embryo and an accessory systemic pulmonary artery in a slightly older embryo measuring 41 mm. He further gives his reasons for differing from the view that during the development of the embryo there is competition for lung tissue between the normal pulmonary and an aberrant pulmonary artery, pointing out that in many cases an accessory systemic pulmonary artery is present without any accompanying abnormality of lung tissue. He therefore concludes, until there is evidence to the contrary, that the concurrent presence of a bronchogenic cyst and a systemic aberrant pulmonary artery is merely coincidental. Bronchogenic cysts arise at an early stage of development and may, it is suggested, be determined by some metabolic abnormality or nutritional deficiency in the mother. Pryce's theory of the "capture" of bronchial buds by "anchored" arteries is discussed at some length.

G. J. Cunningham

1273. **The Pathology of Measles**
G. B. S. ROBERTS and A. D. BAIN. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **76**, 111–118, 1958. 9 figs., 24 refs.

The post-mortem findings are reported in 3 cases of measles in which death occurred during the incubation period of the disease. The characteristic lesion, which was present in all 3 cases, was a giant-cell infiltration of lymphoid tissue. The authors consider that these giant cells probably appear about 7 days before the rash becomes manifest, disappearing shortly after this. Giant-cell pneumonia occurred in one case only; this also

probably disappears in the presence of secondary bacterial invasion. Histological examination of Koplik's spots showed the presence of shallow ulcers associated with an abnormality of the epithelial cells of the buccal mucosa, these cells being arranged in clumps instead of separating normally after mitotic division. It is suggested that this is the primary abnormality in the epithelium and that it renders the epithelium more liable to damage by trauma. *A. W. H. Foxell*

1274. ***In vivo* and *in vitro* Cellular Changes Specific for Measles**
F. E. Sherman and G. Ruckle. *A.M.A. Archives of Pathology* [*A.M.A. Arch. Path.*] **65**, 587–599, June, 1958. 12 figs., 14 refs.

The specific cellular change in fatal cases of measles consists in the formation of reticuloendothelial giant cells and epithelial giant cells. Few fatal cases of measles have been recorded, as early mortality is low and specific changes are usually absent if death occurs after the onset of the rash.

In this paper the necropsy findings and the results of tissue culture and virological studies in 4 fatal cases of measles seen at the Children's Hospital, Pittsburgh, during a 2-year period are reported. Of the 4 patients, 3 died from bacterial bronchitis after the rash had appeared. At necropsy no evidence of measles was found apart from the presence of syncytial giant cells in the vesical mucosa in one case; moreover, no virus was demonstrable on inoculation of tissue extracts into tissue cultures. The remaining patient, whose clinical history is given in detail, died in the prodromal stage without significant secondary infection. Both types of giant cell specific for measles were demonstrated in this case—namely, fused epithelial cells of the respiratory mucosa in the trachea and bronchi and reticuloendothelial giant cells in the lymphoid tissue of lymph nodes, thymus, tonsil, spleen, and intestine, including the appendix. Measles virus was not isolated from the blood or cerebrospinal fluid, but its presence was demonstrated in trypsinized tissue cultures of the spleen, lung, kidney, and lymph nodes. Extracts from various organs were inoculated into pre-grown human amnion cultures, but only the lung extract induced cytopathic changes characteristic of infection with the measles virus.

The authors discuss the origin and fate of these giant cells and their significance in the pathogenesis of measles. They draw attention to the similarity between the cells of measles and those observed in Hecht's giant-cell pneumonia (citing a previously unreported case as evidence), and suggest that " Hecht's pneumonia may be a bizarre form of measles ". *I. Berkinshaw-Smith*

1275. **Primary or Idiopathic Diabetes Insipidus: a System Disease**
H. Blotner. *Metabolism* [*Metabolism*] 7, 191–200, May, 1958. 2 figs., 22 refs.

The author, in this paper from the Beth Israel Hospital, Boston, describes 3 cases of diabetes insipidus in which the only apparent lesion referable to the origin of the symptoms was atrophy of the supraoptic and paraventricular nuclei of the hypothalamus. In each case the disease had been present for a number of years. The only changes found post mortem were a reduction in the size of the posterior lobe of the pituitary gland and, in 2 cases, marked loss of nerve cells of the supraoptic nuclei with partial loss of cells of the paraventricular nuclei. In one case there were no gross lesions in the brain and no general changes were visible on histological examination; the hypothalamic regions were not especially examined in this case. The author states that in 45% of a series of 124 cases of diabetes insipidus there was no clear pathological process to account for the disordered function. He discusses the incidence of inherited diabetes insipidus, and points out that a son of one of his 3 patients had suffered from this disease from birth. In his view it is possible that the pathological changes in hereditary cases " are of the same character as the system degeneration in the idiopathic cases ". He cites from the literature 2 cases of hereditary diabetes insipidus in which there was similar isolated degeneration of the hypothalamic nuclei.

J. B. Cavanagh

1276. **A Histological Study of Dupuytren's Contracture.** (La maladie de Dupuytren. Étude histologique)
C. Nézelof and R. Tubiana. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **34**, 1102–1110, April 18, 1958. 8 figs., 18 refs.

This communication from the Hôpital Cochin, Paris, reports the results of a histological study of material (fragments of fascia and digital nodules) from 25 cases of Dupuytren's contracture. The various staining procedures employed included haematoxylin–eosin–saffron, iron alum, periodic-acid–Schiff (P.A.S.), Masson's trichrome stain, and stains for iron, elastin, metachromasia, and reticulin.

The lesion takes the form of proliferation of the fibrous tissue of the palmar aponeurosis. The authors distinguish two forms of the lesion, which they describe as nodular and lamellar (*forme lamellaire*), although many transitional stages were observed. The nodular form is characterized by the presence of nodular masses of fibroblastic cells containing collagen fibres which stain intensely by the P.A.S. technique and show frequent metachromasia. The lamellar form shows a more regular structure, with few cells; the collagen fibres are thick and often hyalinized, give a negative P.A.S. reaction, and only exceptionally show metachromasia. The authors suggest that the nodular form may represent a relatively recent and still developing stage of the lesion and the lamellar an older and stabilized form. They conclude that although these studies throw no further light on the aetiology of the condition they do at least exclude the possibility of its being inflammatory, rheumatic, or degenerative in nature, and do nothing to sustain the hypothesis of its being a collagen disease.

H. A. Sissons

1277. **Pathologic Changes in the Small Bowel in Idiopathic Sprue; Biopsy and Autopsy Findings**
H. W. Himes and D. Adlersberg. *Gastroenterology* [*Gastroenterology*] **35**, 142–154, Aug., 1958. 5 figs., 16 refs.

Microbiology and Parasitology

1278. **Enteropathogenic Viruses and Bacteria. Role in Summer Diarrheal Diseases of Infancy and Early Childhood**

M. Ramos-Alvarez and A. B. Sabin. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **167**, 147–156, May 10, 1958. 18 refs.

In a study carried out in 1956 at the Children's Hospital, Cincinnati, to determine the role of enteroviruses and of pathogenic bacteria in summer diarrhoea rectal swabs were taken from 97 children with diarrhoea and from 100 children without diarrhoea; 74% of the children were under one year of age. For virus isolation monkey kidney tissue cultures were inoculated with rectal-swab extracts and examined for cytopathic changes, while further tests were made in newborn mice.

Viral agents were isolated from 47 (48%) of the 97 children with diarrhoea and from 20 (20%) of the 100 children without diarrhoea. The strains were identified as follows: E.C.H.O. virus (from 31% of the diarrhoeal cases and 5% of the non-diarrhoeal); poliomyelitis virus (3% and 3%); Coxsackie virus (4% and 6%); adenoviruses (3% and *nil*); unclassified mouse-pathogenic strains (1% and *nil*). The serological types of the strains of E.C.H.O. virus from the diarrhoeal cases were: Type 6 in 5 cases, Type 7 in 11, Type 8 in 2, Type 14 in 5, and unclassified in 7. (Six of these unclassified strains were later found to form 3 new antigenic E.C.H.O. types.) Of the 5 E.C.H.O. virus strains from the children without diarrhoea, one was of Type 2, 3 of Type 7, and one of Type 14. These results were similar to those of a preliminary study made in 1955 on 56 children with diarrhoea, when E.C.H.O. virus strains were isolated from 12 (21%). These were of Type 2 in one case, Type 8 in one, Type 11 in 2, Type 12 in 3, a variant of Type 6 in 2, a variant of Type 10 in one, and one case each of 2 new antigenic types, 18 and 19. Coxsackie virus was isolated from 5 (9%) of these 56 children, poliomyelitis virus from 3 (5%), adenoviruses from 1 (2%), and unclassified mouse-pathogenic strains from 3 (5%).

In the 1956 study *Shigella* or *Salmonella* was isolated from 6 (7%) of 86 children with diarrhoea, but from none of 64 children without diarrhoea. The incidence of all enteropathogenic types of *Escherichia coli* was not significantly different in the two groups of children. It was found, however, that Type O111B4 (with 16 isolations) and Type O55B5 (with 5 isolations) predominated among the 26 pathogenic strains of *Esch. coli* isolated from 86 children with diarrhoea. Type O111B4 was 6 times more frequent in the diarrhoeal than in the non-diarrhoeal group. Of 13 pathogenic strains of *Esch. coli* isolated from 64 children without diarrhoea, 6 were of Type O125B15 or O119B14, which types were not isolated from any of the children with diarrhoea. Double infections with enteropathogenic viruses and bacteria were found in 15% of children with diarrhoea.

Severe illness was most frequent among children infected with enteropathogenic *Esch. coli*, either alone or in combination with viruses, and was least frequent among those from whom only viruses were isolated. Limited serological tests indicated that acute virus infections also occurred in 20% of children from whom no virus could be isolated. In acute-phase sera from 24 children little or no antibody was found against the virus isolated, but antibody appeared in varying titres during convalescence. *Joyce Wright*

1279. **Relationship of Measles and Distemper**

J. M. Adams, D. T. Imagawa, D. L. Chadwick, E. H. Gates, and R. A. Siem. *A.M.A. Journal of Diseases of Children* [*A.M.A. J. Dis. Child.*] **95**, 601–608, June, 1958. 5 figs., 31 refs.

The measles virus and the canine distemper virus have both been adapted to suckling mice, although not yet to the same cell lines, and experimental measles has been successfully produced in puppies. This paper presents data of a pathological nature from human cases of measles and experimental distemper in animals. The human measles pathological material was obtained from two patients who died of infection by measles virus. Susceptible ferrets were inoculated with the Lederle strain of ferret-adapted distemper virus and were killed at various stages in order that the development of the pathological changes might be studied. The authors draw attention to certain clear-cut clinical similarities between these two diseases, in particular identical incubation periods, high infectivity, respiratory symptoms, rashes, and demyelinating encephalitis. Their present studies demonstrate further pathological and immunological relationships, which are illustrated by comparative photomicrographs and the results of neutralization tests in tissue culture and animals. These results suggest that common antigenic components are shared by the viruses of measles and distemper. *J. M. Smellie*

1280. **The New ECHO Viruses and Their Role in Human Disease.** [Review Article]

D. M. Horstmann. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **102**, 155–162, July, 1958. 3 figs., 19 refs.

1281. **Staining Bacterial Smears with Fluorescent Antibody. IV. Grouping Streptococci with Fluorescent Antibody**

M. D. Moody, E. C. Ellis, and E. L. Updyke. *Journal of Bacteriology* [*J. Bact.*] **75**, 553–560, May, 1958. 2 figs., 8 refs.

In experiments carried out at the Communicable Disease Center of the U.S. Public Health Service, Atlanta, Georgia, globulin fractions were prepared from streptococcal group-specific precipitating antisera and

conjugated with fluorescein *iso*cyanate. It was found that dried smears of β-haemolytic streptococci showed marked fluorescence when treated with the conjugated antibody. Such fluorescence would occur even when the antibody was in high dilution. Most of the work was carried out with Group-A antibody, and good fluorescence was obtained with all the Group-A strains tested with it, but none with strains of Groups B, D, and F. Fluorescence was, however, obtained with strains of Groups C and G treated with Group-A antibody. These cross-reactions could be abolished by previous absorption of the antibody with a suspension of Group-C organisms. Specific reactions were also obtained when organisms of Groups B, C, D, F, and G were treated with the homologous conjugated antibody. Because of the speed with which the groups may be determined by this method an attempt was made to apply it to the identification of the streptococci in pathological material. Although the number of cases studied is too small as yet for firm conclusions to be drawn, there seems little doubt that it will prove valuable. *R. Hare*

1282. **Enteropathogenic Effects of Strains of *Bacterium coli* Isolated from Cases of Gastroenteritis**
W. McNaught and G. B. S. Roberts. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **76**, 155–158, 1958. 3 figs., 4 refs.

In experiments designed to ascertain whether the serotypes of *Escherichia coli* associated with infantile gastro-enteritis would cause lesions in the rabbit bowel, ligated loops of adult rabbit's small intestine were injected with 2 ml. of a 24-hour culture of *Esch. coli* in peptone water; 24 hours later all animals were killed and the loop examined macroscopically and microscopically. Of 7 typable strains of *Esch. coli* (2 Type O26B6, one of Type O55B5, 3 of Type O111B4, and one of Type O125B15) isolated from infants without symptoms of gastro-enteritis, one type only (O111B4) produced a significant, and severe, histological change, whereas of 16 typable strains of *Esch. coli* isolated from infants (and one adult) with gastro-enteritis, 13 (81%) produced lesions in the ligated bowel loops. Seven of these strains (2 of O26B6, one of O55B5, and 4 of O111B4) produced a severe type of tissue reaction characterized by necrosis and ulceration of the mucosa, with marked infiltration of polymorphonuclear leucocytes in the mucosa and muscle coats; 6 strains (one of O55B5, 4 of O111B4, and one of O125B15) produced oedema in the villi and submucosa, while 3 strains (2 of O26B6 and one of O55B5) produced no histopathogenic effects. Of these 16 strains, 9 had been isolated from babies with severe gastro-enteritis and 7 from mild cases. It was observed that the degree of reaction in the rabbit bowel did not give an indication of the severity, as distinct from the presence, of the gastro-enteritis.

In control experiments no essential deviation from normal rabbit bowel structure was found following (1) ligation alone, (2) ligation plus injection of sterile peptone water, or (3) ligation with injection of 4 untypable strains of *Esch. coli* isolated from healthy infants.
Joyce Wright

1283. **Circulating Antibodies in Sarcoidosis**
R. Greenwood, H. Smellie, M. Barr, and A. C. Cunliffe. *British Medical Journal* [*Brit. med. J.*] **1**, 1388–1391, June 14, 1958. 15 refs.

From King's College Hospital, London, a study is reported of circulating antibody production in patients with sarcoidosis after immunization with tetanus toxoid. The patients received an intramuscular injection of 1 ml. of tetanus toxoid and a similar injection 6 weeks later.

A normal circulating antibody response was noted in 10 patients with sarcoidosis who had been immunized against tetanus some years earlier. Primary immunization was carried out on 12 patients with sarcoidosis, 8 with reticulosis, and 14 controls. The patients with sarcoidosis showed significantly less circulating antitoxin than did the controls, the response being poorest in those in whom the sarcoid process was "active". Of the 8 patients with reticulosis, 4 showed no detectable antibody response. The natural staphylococcal alpha-antitoxin titres of the serum of 50 patients with sarcoidosis and of 19 with reticulosis were of the same order as that of 75 controls. *D. Geraint James*

1284. **Hydatid Complement-fixation Test: Influence of Intermediate Host Protein on Specificity of Sheep Hydatid Fluid Antigen**
H. J. Bensted and J. D. Atkinson. *British Medical Journal* [*Brit. med. J.*] **2**, 203–205, July 26, 1958. 7 refs.

The complement-fixation test for hydatid disease has always been regarded as highly specific, but in a series of 300 tests performed on sera from suspected cases at the Central Public Health Laboratory, Colindale, London, a false positive result was obtained in a fatal case of carcinoma of the lung, whereas in 12 similar cases the result was negative. It transpired that the patient giving the false positive reaction had recently been given a full course of sheep-brain anti-rabies vaccine, and a similar case was subsequently encountered in which partial fixation of complement in the test for hydatid disease was associated with a past history of anti-rabies vaccination.

After inconclusive tests with rabbits and guinea-pigs had been carried out 5 human volunteers, all of whom had in the past had one or more courses of anti-rabies vaccine, were subjected repeatedly to the Casoni test (intradermal injection of sheep hydatid fluid), which produced a definite local reaction in one case only. After 2 or 3 injections 3 out of the 5 developed significant amounts of complement-fixing antibody to sheep protein and one to hydatid antigen. Later, sera from 3 patients in Hong Kong who had received courses of anti-rabies vaccine more recently were obtained and the hydatid complement-fixation test performed on them, with positive results in 2 cases and a doubtful result in one.

These findings confirm that the use of an antigen containing both the host protein and the specific hydatid fractions in testing for hydatid disease may cause confusion in patients previously immunized with vaccines containing the same or related host proteins.
Clement C. Chesterman

Pharmacology and Therapeutics

1285. **The Influence of Carbon Dioxide on the Neuromuscular Blocking Activity of Relaxant Drugs in the Cat**
J. P. PAYNE. *British Journal of Anaesthesia* [*Brit. J. Anaesth.*] **30**, 206–216, May, 1958. 14 figs., 19 refs.

Clinical experience of the use of relaxant drugs during anaesthesia has shown that their action can be prolonged by over-ventilation, suggesting that the converse may also be true, namely, that their action may be diminished by accumulation of carbon dioxide. To test this hypothesis experiments were carried out in the Department of Pharmacology of the Royal College of Surgeons of England, London, in which the sciatic-nerve–tibialis-anterior preparation of the intact cat was used. The animals were anaesthetized with chloralose and intubated, and artificial respiration was established. Various relaxant drugs were then given in standard doses and their effects on the response of the muscle to repeated stimulation of the sciatic nerve (which was recorded on a smoked drum) were observed before, during, and after the administration of carbon dioxide in concentrations of 5%, 10%, and 20% for periods of 20 to 45 minutes.

Carbon dioxide under these conditions was found to antagonize the action of suxamethonium, decamethonium, and gallamine, and to enhance the action of tubocurarine. It is suggested that changes in the degree of ionization and protein-binding power of the drugs as a result of changes in the *p*H of the blood may be responsible for the effect of carbon dioxide on their neuromuscular blocking activity. *Ronald Woolmer*

1286. **Antihistaminic Drugs.** [Review Article]
A. L. MICHELSON and F. C. LOWELL. *New England Journal of Medicine* [*New Engl. J. Med.*] **258**, 994–1000, May 15, 1958. 1 fig., bibliography.

1287. **The Pharmacology of Propionyl Atropine Methyl Nitrate**
L. HERMAN, F. H. SHAW, and E. I. ROSENBLUM. *Journal of Pharmacy and Pharmacology* [*J. Pharm. (Lond.)*] **10**, 348–355, June, 1958. 1 fig., 7 refs.

From the Department of Pharmacology, University of Melbourne, the authors describe the results of pharmacological studies of a series of esters of atropine and hyoscine, both in the tertiary and in the quaternary forms, in regard to their muscarinic, ganglion-blocking and neuromuscular transmission-inhibiting activities and to their effect on gastric secretion. The spasmolytic potency of each of the 10 drugs tested was compared with that of atropine in its power to inhibit acetylcholine-induced spasms of the guinea-pig isolated ileum. The anticholinergic activity of hyoscine was found to be about twice that of atropine, and esterification did not affect the activity quantitatively or qualitatively; quaternization of the esters, however, as in the case of propionyl atropine methyl nitrate (P.A.M.N.) decreased the spasmolytic activity. In tests on the prepared superior cervical ganglion of the cat P.A.M.N. was shown to have marked ganglionic-blocking activity, which was not, however, as powerful as that of pentamethonium; the site of action of P.A.M.N. was shown to be at the ganglion. All the compounds tested produced some fall in blood pressure, but 6 paraplegic patients receiving about 24 mg. daily for 6 months had no symptoms of orthostatic hypotension.

The effect on gastric secretion was studied in the rat. Since gastric secretion stops in the unconscious animal the anaesthetized animals were roused with an intraperitoneal injection of bemegride before the test drug was injected subcutaneously. The total volume and acidity of gastric secretion were decreased for periods of 18 to 22 hours after a single subcutaneous injection, atropine compounds having more powerful antisecretory activity than the hyoscine compounds and the quaternary derivatives being more active than the tertiary. P.A.M.N. had a curariform action at the neuromuscular junction, in man, but no patient complained of muscle weakness. In regard to toxicity, when given intraperitoneally P.A.M.N. was three times as toxic as atropine, but administered by mouth it was only half as toxic. This apparently paradoxical finding confirms that the quaternary compounds are more toxic than the tertiary when given parenterally, but less when given orally. The authors consider that P.A.M.N. shows promise as an agent for the symptomatic treatment of peptic ulceration. The compounds studied in this investigation were atropine sulphate, atropine methyl bromide, hyoscine hydrobromide, propionyl atropine methyl nitrate, valeryl atropine methyl bromide, hyoscine methyl bromide, N-butyryl hyoscine bromide (" buscopan "), oxyphenonium (" antrenyl "), pipenzolate (" piptal "), and pentamethonium. The detailed results are presented in a number of tables. *T. J. Thomson*

1288. **The Action of Propionyl Atropine Methyl Nitrate on Gastric Function**
L. HERMAN and F. H. SHAW. *Journal of Pharmacy and Pharmacology* [*J. Pharm. (Lond.)*] **10**, 356–362, June, 1958. 3 figs., 4 refs.

In this further study carried out at the University of Melbourne [see Abstract 1287] the authors have investigated more fully the effects of the quaternary ammonium ester of atropine, propionyl atropine methyl nitrate (P.A.M.N.), on gastric secretion and gastric motility in man. The antisecretory effect of a single oral dose of the test drug was measured by noting the secretory response to an alcohol test meal. After the patient had fasted for 8 hours the stomach was emptied completely, and the warmed test meal, with or without the drug under trial, was passed down a Rehfuss tube. A 10-ml. sample of the gastric contents was withdrawn immedi-

ately and thereafter at 15-minute intervals for 2 to 2½ hours. The free acidity, total acidity, and *p*H of each sample were estimated, the results being expressed as the amount of 0·1 N sodium hydroxide in ml. required to neutralize 100 ml. of gastric content. The effect of P.A.M.N. was compared with those of atropine and atropine methyl bromide in 76 experiments on 6 subjects, each patient serving as his own control. All subjects in whom 0·65 mg. of atropine caused a rise in gastric *p*H and a decrease in acid secretion showed a reaction to the quaternary derivative which was more pronounced and of longer duration. Difficulty in obtaining the later samples was experienced only in those patients who had received the quaternary derivative.

The effects of P.A.M.N. on gastric motility were assessed indirectly, using a variation of the glucose tolerance test. Some 30 to 45 minutes after swallowing the test drug in the form of a tablet the subject took 50 g. of glucose in 100 ml. of water. Samples of capillary blood were taken immediately before the glucose and on 5 occasions thereafter at 15-minute intervals, the glucose content of the blood samples being estimated colorimetrically by means of a Beckman spectrophotometer. As a result of 100 experiments on 8 subjects P.A.M.N. was found to be active in 7 of the 8, producing blood sugar levels which were lower than the control readings in the same subjects; the 8th subject was a diabetic. In 2 of these subjects 0·65 mg. of atropine was shown to be about two-thirds as effective as P.A.M.N. In 10 volunteer subjects given a single dose of 6 mg. of P.A.M.N. orally there was no significant effect on the blood pressure or heart rate during the following 3 hours. Clinical trials with 6 mg. of P.A.M.N. 6-hourly on 26 patients with peptic ulcer failed to reveal any undesirable side-effects or disturbance of micturition, and alleviation of symptoms was satisfactory. Six of these patients have been treated for up to 6 months, but no sign of tolerance has appeared. *T. J. Thomson*

1289. **Adrenochrome Monosemicarbazone (Adrenoxyl). An Interim Evaluation of Its Effect in Reducing Blood Loss**

J. S. RUDDELL. *Anaesthesia* [*Anaesthesia*] **13**, 269–278, July, 1958. 6 figs., 3 refs.

Adrenoxyl (adrenochrome monosemicarbazone) is a stable form of adrenochrome, a substance which has been shown to produce effective capillary haemostasis. In investigations carried out at the City General Hospital, Gloucester, in an attempt to confirm the definite clinical impression that adrenoxyl reduces bleeding without affecting blood coagulation, the author first studied the haematocrit values in patients before and again 24 hours after undergoing a surgical operation, no intravenous fluids having been given in the interim. This showed that there was no change in the haematocrit value in patients operated on with a tourniquet, whereas this value fell by a mean of 4% in patients who received adrenoxyl and by a mean of about 8% in those who did not receive the drug.

In further studies carried out on 12 unanaesthetized rabbits 20 small incisions were made in the posterior surface of the right ear, the average of the bleeding times for these 20 lesions being taken as the control mean bleeding time. Adrenoxyl (5 μg. per kg. body weight) was then injected intravenously and a further 20 similar incisions made in the posterior surface of the left ear, the mean bleeding times being estimated as before. The mean bleeding time after adrenoxyl (1 minute 9 seconds) was significantly shorter than the control time (2 minutes 19 seconds). The author considers that adrenoxyl premedication should be given as a routine before all operations not being performed under a tourniquet, and that this drug would be particularly useful in the fields of obstetrics and dentistry. *Mark Swerdlow*

1290. **Mechanism of Action of Norepinephrine in Hemorrhagic Shock**

A. M. LANSING and J. A. F. STEVENSON. *American Journal of Physiology* [*Amer. J. Physiol.*] **193**, 289–293, May, 1958. 1 fig., 19 refs.

In this study of the action of adrenaline in experimental shock, carried out at the University of Western Ontario, London, Ontario, 29 dogs were anaesthetized with pentobarbitone and shock was rapidly produced by bleeding from the carotid artery (the blood being collected in a reservoir) so that the mean arterial pressure measured at heart level was lowered to 35 to 40 mm. Hg in 10 minutes. The hypotensive state was continued at this level until a fall in peripheral arterial pressure occurred, at which point a clamp was placed on the tubing leading from the carotid artery to the reservoir—that is, bleeding was stopped and automatic reinfusion begun, all the blood collected in the reservoir being reinfused via the femoral artery within 10 minutes by a multiple-syringe technique. The blood pressure, pulse rate, and pulse-wave contour were recorded by electromanometer from the femoral artery, oxygen consumption was measured with a Sanborn " metabulator ", the cardiac output was calculated by the direct Fick procedure, and the total peripheral resistance was estimated from the electrically integrated mean arterial pressure and the cardiac output. Plasma volume was determined with radioactive iodinated human serum albumin in 16 dogs and the plasma catechol amine level in 19. At 15 minutes after completion of the reinfusion a constant infusion of noradrenaline in a dose of 4 μg. per minute in 5% glucose (infused at a rate of 15 ml. per hour) through the cardiac catheter was begun in 15 of the dogs, the other 14 receiving the 5% glucose solution only and serving as controls. After completion of the surgical procedures, no more anaesthetic was administered.

Of the control group of animals, only 2 survived for 48 hours, whereas 6 of the test group survived. The cardiac output fell in both groups of animals after bleeding, but the fall in the dogs receiving noradrenaline was less than in the controls and was not significant. The total peripheral resistance rose in the controls, but in the dogs given noradrenaline it was not significantly different from the normal. The oxygen consumption fell at first in both groups, but began to rise between 4 and 8 hours after reinfusion, and was then considerably greater in the adrenaline-treated animals than in the controls. The

plasma volume fell in both groups. It is concluded from this study that noradrenaline maintains arterial pressure not by increasing the peripheral resistance, but rather by maintaining the cardiac output.

P. A. Nasmyth

1291. **Pharmacology and Clinical Use of Pempidine in the Treatment of Hypertension**
K. HARINGTON, P. KINCAID-SMITH, and M. D. MILNE. *Lancet* [*Lancet*] **2**, 6–11, July 5, 1958. 5 figs., 21 refs.

" Pempidine " (1:2:2:6:6-pentamethylpiperidine), a tertiary amine, is a new ganglion-blocking agent with properties similar to those of mecamylamine. At Hammersmith Hospital, London, the pharmacology of the drug was studied in 32 hypertensive patients, 27 of whom received continuous treatment. The hydrochloride was used for intravenous injection and the bitartrate for oral administration.

Pempidine was completely absorbed from the gut and eliminated in the urine, the excretion being delayed by renal failure. The excretion of pempidine was about twice as rapid as that of mecamylamine in urine of normal *p*H; it was reduced by alkalinization of the urine and hastened by acidification, but was less influenced by the *p*H than was excretion of mecamylamine. The concentration of pempidine in the blood was low, and the drug was not bound to the plasma proteins. It readily crossed cell membranes and was concentrated in nuclear tissues. Intravenous injection of 5 mg. of the hydrochloride in 21 recumbent hypertensive patients was followed by a fall in blood pressure usually within 2 minutes; postural hypotension persisted for 2 to 6 hours after the injection. In 9 patients given a single oral dose of 5 to 20 mg. of the bitartrate a hypotensive effect usually appeared within one hour and persisted for 6 to 7 hours afterwards.

Pempidine was given to 27 patients with severe hypertension of various types in an initial dosage of 2·5 mg. 4 times daily, increased by 2·5 mg. per dose per day until a satisfactory therapeutic response was achieved; the average total daily dose was 32·5 mg. (range 5 to 100 mg.). A stable effective dose of the drug was rapidly reached and tolerance was not observed. Treatment was continued for an average period of 10 weeks (range 2 to 20 weeks.) Reserpine and chlorothiazide appeared to potentiate the hypotensive action of pempidine. Side-effects were similar to those observed with other ganglion-blocking agents, and disappeared promptly when a dose was omitted.

Bernard Isaacs

1292. **Reaction of the Cardiac Vasculature to Drugs in Coronary Insufficiency.** (Реактивность сосудов сердца человека при коронарной недостаточности)
JU. S. ČEČULIN. *Архив Патологии* [*Arh. Patol.*] **20**, 40–44, No. 4, 1958. 2 figs., 8 refs.

The topical action of euphylline (aminophylline) and nitroglycerin on the coronary circulation was studied at the Institute of Pharmacology, Moscow, by the method of Kulyabko on 39 isolated human hearts within 7 to 37 hours of the subject's death; of these hearts, 13 were from persons who died of trauma and served as normal controls, while the remaining 26 were from patients who died either of cardiac infarction or during an anginal attack (" coronary " hearts). The hearts were perfused, under a constant pressure of 70 mm. Hg with various concentrations of aminophylline or nitroglycerin, and alterations in the volume of coronary flow, as indicated by the amount of fluid escaping on the venous side, were recorded kymographically.

Aminophylline in concentrations of 1:2,000 to 1:5,000 produced vasodilatation in 23 of the 26 " coronary " hearts, but only in 8 of 13 control hearts; in the remaining cases vasoconstriction of the coronary arteries occurred. With nitroglycerin in concentrations ranging from 1:300,000 to 1:2,000,000 vasodilatation was observed in 14 of 18 " coronary " hearts and in 8 out of 9 controls, while in 3 of the remaining " coronary " hearts no effect was noted. Vascular changes in infarcted hearts were weak and sluggish. In the hearts of patients dying from coronary insufficiency the vascular reaction was usually biphasic, transient vasoconstriction preceding the more stable phase of vasodilatation.

A. Swan

1293. **Some Cardiovascular Effects of Reserpine**
M. D. YABLONSKI, A. M. STOCKMAN, F. S. CALIVA, and R. H. LYONS. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **235**, 639–643, June, 1958. 15 refs.

To determine whether the hypotensive effect of reserpine is associated with alterations in vasoconstrictor tone digital blood flow was directly measured by venous occlusion plethysmography before and after parenteral administration of the drug in 5 normotensive and 7 hypertensive patients at Upstate Medical Center, State University of New York, Syracuse. The digital blood flow was recorded during a control period, at 4 hours after an intramuscular injection of 2·5 mg. of reserpine, and after posterior tibial nerve block.

The resting blood flow in normotensive patients was similar to that in hypertensive patients; in both groups there was a significant increase after administration of reserpine and a much larger increase following sympathetic block. In both groups there were significant falls in blood pressure and in " peripheral resistance " (assessed arbitrarily by dividing mean blood pressure by blood flow), but there was no change in pulse rate. Postural hypertension, dizziness, conjunctival injection, and nasal congestion were among the side-effects.

The authors conclude that reserpine causes a decrease in vasoconstrictor tone with a consequent fall in peripheral resistance.

Gerald Sandler

1294. **Clinical Comparison of Six Digitalis Preparations by the Parenteral Route**
C. ARAVANIS and A. A. LUISADA. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **1**, 706–716, June, 1958. 19 refs.

The clinical effects by the parenteral route of 6 digitalis preparations—digitoxin (digitaline) (0·8 mg.), acetyldigitoxin (" acylanid ") (0·8 mg.), digoxin (" lanoxin ") (1 to 1·5 mg.), deslanoside (" cedilanid D ") (1·5 mg.), gitalin (" gitaligin ") (3 mg.), and ouabain (" ouabaine ")

(0·5 mg.)—in cases of heart failure were compared at Mount Sinai Hospital (Chicago Medical School), Chicago. Only digitoxin could be given intramuscularly without pain, so the other drugs were given by intravenous injection. In general, a single daily injection was administered, but ouabain had to be given in two daily doses because of serious toxic effects when the dosage required was given in a single daily injection. Each drug was given to 21 patients, with initial digitalization over 2 to 3 days and a total observation period of 7 days. (The doses stated above are those given on the first day of treatment, the final maintenance doses ranging from one-half to one-twelfth of these figures.) The patients were suffering from various forms of heart disease, most of them ischaemic, hypertensive, or rheumatic, and their ages ranged from 21 to 90 (average 65) years. None had received any digitalis preparation during the previous 14 days.

Deslanoside and digoxin produced the greatest average slowing of the pulse, though it is pointed out that 119 out of 136 patients were in sinus rhythm and this finding might not be valid for patients with atrial fibrillation. Ouabain and digitoxin produced the most rapid clinical improvement (within 2 days). Objective improvement, as assessed from lowering of venous pressure and circulation time and reduction of the heart size (measured radiologically), was faster with digoxin, digitoxin, and acetyldigitoxin than with the other 3 drugs. Digitoxin produced the most marked electrocardiographic (ECG) changes, and ouabain the most marked toxic effects. An over-all rating based on all the above criteria of assessment with the exception of ECG changes gave first place equally to digitoxin and acetyldigitoxin and last place to ouabain. This, however, should not be unduly stressed, there being special indications for several glycosides. Thus ouabain is still the best preparation available for obtaining rapid improvement, its effect being complete within 2 hours. Digitoxin is almost as rapid in action, its effect being complete within 6 hours, and has the advantage that it can be given painlessly intramuscularly and is as effective by this route as intravenously. But although it shows little toxicity and achieves first place in over-all rating, it has the greatest effect of any of the drugs tested on the ECG. For long-term treatment digoxin or deslanoside might therefore be preferable because of the less marked ECG changes which they induce. *David Phear*

1295. **Clinical Evaluation of Acetyldigitoxin**
J. B. VACCA, J. M. SCHUSTER, and W. A. KNIGHT. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **1**, 717–722, June, 1958. 3 figs., 9 refs.

Acetyldigitoxin is prepared from *Digitalis lanata* and has promising pharmacological properties, being an active cardiac glycoside, well absorbed, and less cumulative and less toxic than digitoxin. Experience with this drug, given by mouth, in the treatment of 35 in-patients is described in this paper from St. Louis University School of Medicine, St. Louis, Missouri. The patients ranged in age from 40 to 90 years and all but 5 were suffering from arteriosclerotic or hypertensive heart disease or cor pulmonale. They were selected " only on the basis of the presence of indications for digitalization".

In 32 cases acetyldigitoxin was used for initial digitalization, the remaining 3 patients being already under maintenance treatment with other digitalis preparations for which acetyldigitoxin was substituted. During digitalization a dose of 0·2 mg. 4-hourly or 0·4 mg. 6-hourly was used, according to the urgency of the case. In the 7 patients with auricular fibrillation the ventricular rate was used as a guide in treatment, while in the presence of sinus rhythm digitalization was continued until significant diuresis occurred or early toxic effects, mainly anorexia and nausea, developed. Clinical progress was assessed from changes in the symptoms, body weight, physical signs, and electrocardiogram, and in many cases from serial estimations of vital capacity, venous pressure, and circulation time and from radiographs of the chest.

Acetyldigitoxin proved to be a safe and effective drug. In only 4 cases was congestive failure not improved and in 3 of these complicating factors were present. The drug's action begins 2 hours after an oral dose and its effect reaches a maximum after 8 to 16 hours. Most patients required between 1·4 and 2 mg. over 24 hours for full digitalization, though a few required up to 4 mg. The daily maintenance dose in 15 of the 16 cases in which treatment was continued for some months was 0·1 to 0·2 mg., and in one case 0·3 mg. Toxic effects were mild; anorexia and nausea were usually the first to appear, providing a useful warning before more serious cardiac effects developed and almost always disappearing within 1 to 3 days of stopping the drug. One patient developed transient auricular tachycardia and 3 auricular fibrillation during treatment. *David Phear*

1296. **Clinical Evaluation of Intramuscular Digitoxin in the Management of Congestive Heart Failure**
N. A. DE FRANCIS, J. KLEMENTS, and A. GORDON. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **1**, 723–725, June, 1958. 5 refs.

Oral administration of digitalis preparations may be impossible because of vomiting, gastro-intestinal disease, coma, or lack of cooperation. On the other hand intravenous injection is risky and is only justified when speed is essential, while in an oedematous patient the veins may be difficult to locate. The introduction of a preparation of digitoxin suitable for intramuscular injection is therefore welcome. In this preparation, " digitaline nativelle intramuscular " (Strauss *et al.*, *Amer. Heart J.*, 1952, **44**, 787), digitoxin is dissolved in a vehicle consisting of polyethylene glycol 300 (28·6%), glycerin (43·8%), benzyl alcohol (4%), ethyl alcohol (5%), and water. The present authors describe the successful use of this solution, given intramuscularly, in the treatment at the Triboro Hospital, New York, of 36 patients aged 29 to 83 years with congestive failure, 23 of whom had auricular fibrillation. Rheumatic heart disease was present in 6 cases, hypertensive disease in 9, and arteriosclerotic disease in 21. Venous pressure measurement, chest radiography, electrocardiography, and ballistocardiography were used in assessing progress.

For initial digitalization 0·6 mg. of digitoxin was injected in 2 equal doses. After 4 hours the patient's condition was reassessed and, as required, 0·2-mg. doses were given at 4-hour intervals until signs of congestive failure subsided or S–T depression and T-wave inversion developed in the electrocardiogram. A daily maintenance dose was then given for 10 days, when treatment was discontinued, signs of failure returning within 2 to 9 days. The dose required for digitalization varied from 1·2 to 2 (average 1·4) mg. An effect was noticeable 4 hours after the initial injection, when the average ventricular rate had fallen from 102 to 82 per minute and the average venous pressure from 224 to 168 mm. H_2O. The average daily maintenance dose was 0·2 mg. The same dose is equally effective by mouth and by injection, so that administration can be conveniently changed from one route to the other. Congestive failure was effectively controlled in all cases. About half the patients noticed some muscle pain, but there were no local complications from the injection. *David Phear*

1297. **Intramuscular Iron Therapy with Iron–Dextran**
B. J. KOSZEWSKI and J. R. WALSH. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **235**, 523–531, May, 1958. 1 fig., 29 refs.

Intramuscular injections of an iron–dextran complex were tried in the treatment of iron-deficiency anaemia in 18 patients at the Creighton Memorial St. Joseph's Hospital, Omaha. The ages of the patients ranged from 9 to 79 years, and in most of them the anaemia was due to blood loss. The initial haemoglobin level varied from 5·4 g. to 10·3 g. per 100 ml. The total dose of iron was calculated on the assumption that 250 mg. would raise the haemoglobin level by 1 g. per 100 ml.

Most of the patients showed a satisfactory response to the injections. The source of haemorrhage could not be eliminated in 3 patients and they became anaemic again after the initial improvement. Clinical improvement was evident after 4 to 5 days, lassitude, dyspnoea, and palpitation disappearing progressively. The increase in the haemoglobin level in the first two weeks varied from 0·3 g. to 1·8 g. per 100 ml., and from the third week onwards averaged 0·8 g. per 100 ml. Normal levels were reached in 5 to 16 weeks. In 3 cases there was a marked eosinophilia, but no other changes in the leucocyte count were observed. The serum iron level usually increased on the second or third day and continued to rise steadily during the entire treatment period, declining after the injections were discontinued. The maximum serum iron level varied from 235 μg. to 1,020 μg. per 100 ml. The incidence of side-effects was low: only 2 patients complained of local pain, no tissue necrosis was evident clinically or in punch biopsy specimens, and skin discoloration was rare. General reactions were also mild: 2 patients had a skin rash which responded to administration of antihistamine drugs, 3 had diarrhoea, and one patient experienced a shock-like condition after the first injection, but not following subsequent injections.

The authors discuss the merits of parenteral iron therapy. In their view, although the response after intramuscular administration is slightly slower than that following intravenous injection, the former is to be preferred to the latter. They consider that the indications for parenteral iron therapy are: (1) poor absorption of iron when taken by mouth; (2) the presence of gastro-intestinal disorders which may be aggravated by oral medication; and (3) intolerance of iron when given by mouth. Parenteral administration is also indicated for those patients in whom it is necessary to replace iron stores in a short time, and is to be preferred to blood transfusion for correcting the effects of chronic blood loss. It is emphasized that the possible danger of systemic haemosiderosis can be avoided by adhering to the recommended dosage. *R. F. Jennison*

1298. **Further Clinical Trials of Oral Diuretics of the Aminouracil Group (Mictine, Rolicton) Compared with the Diuretic Effect of Theophylline.** [In English]
N. I. NISSEN and B. ZACHAU-CHRISTIANSEN. *Acta medica Scandinavica* [*Acta med. scand.*] **160**, 385–395, April 15, 1958. 3 figs., 17 refs.

With a reference to the work of Platts and Hanley (*Brit. med. J.*, 1956, **1**, 1078; *Abstr. Wld Med.*, 1956, **20**, 366) and to their own previous study (*Acta med. scand.*, 1956, **154**, 349; *Abstr. Wld Med.*, 1957, **21**, 79) the authors now report from the Frederiksberg Hospital, Copenhagen, further comparative studies of three oral diuretic drugs in the treatment of cardiac oedema. The drugs and their doses were: (1) theophylline, 800 mg. daily; (2) aminometradine ("mictine"), 800 mg. daily; and (3) methallyl-methyl-aminouracil (amisometradine; "rolicton"), 1,600 to 4,800 mg. daily. The first two drugs were administered for 3 consecutive days each week and a "diuresis quotient" was determined, this being the ratio of the mean daily urinary output during drug therapy to the previously observed basal urine output. For aminometradine, which was administered to 107 patients, the mean diuresis quotient was 1·68, and for theophylline (66 patients) it was 1·51, which is said to be significantly lower; about one-quarter of the patients in each of these two groups experienced gastro-intestinal side-effects. Amisometradine was administered to only 12 patients; the records, though still incomplete, suggested that the diuretic effect of this drug appeared to be at least as great as that of aminometradine, while side-effects with it were uncommon.

Biochemical studies on 20 patients who received aminometradine and amisometradine showed that both drugs caused a relatively greater excretion of sodium and chloride than of water, and that the increased excretion of potassium was similar to that of water, while the excretion of chloride was found to be greater than that of sodium.

[The value of the statistical analysis of these results is lessened, if not entirely vitiated, by the authors' habit of excluding from analysis all cases in which no increased diuresis resulted from the use of the drugs.]
Bernard Isaacs

1299. **Psychotomimetic Drugs**
H. K. BEECHER, *Journal of Chronic Diseases* [*J. chron. Dis.*] **8**, 253–285, Aug., 1958. Bibliography.

Chemotherapy

1300. **Antibiotic Combinations. Antibacterial Action of Plasma of Human Subjects after Ingestion of Penicillin V or Chloramphenicol or Both**
M. FINLAND, C. V. PRYLES, and W. F. JONES. *New England Journal of Medicine* [*New Engl. J. Med.*] **258**, 817–824, April 24, 1958. 5 figs., 41 refs.

The literature on the combined action of chloramphenicol and penicillin is reviewed. Most observers have demonstrated interference (antagonism) of chloramphenicol with the antibacterial action of penicillin *in vitro* and with its therapeutic action on experimental infections, but others have noted no such antagonism, and even synergistic effects have been reported by some authors.

In the present study plasmas of 6 normal men obtained at intervals after the ingestion of single doses of chloramphenicol or penicillin V or both were assayed for antibacterial action against 5 test organisms. No evidence of interaction of these antibiotics was revealed. A combined dose of 0·5 g. of each antibiotic produced activity in the plasma against *Streptococcus* 98, pneumococcus Type 2 and *Staph.* 209P that was no greater, on the average, than was found after a single dose of 0·5 g. of penicillin V alone. Neither the single doses of 1·0 or 0·5 g. of the individual antibiotics nor the combination of 0·5 g. of each enhanced the normal antibacterial action of the plasma of 5 of these subjects against the test strains of *Escherichia coli* and *Klebsiella pneumoniae*.

It may be concluded that the combined action of chloramphenicol and penicillin is probably of no clinical significance.—[Authors' summary.]

1301. **Triacetyloleandomycin and Erythromycin in Serum. Comparison of Concentrations and of Antibacterial Effects**
A. J. REISCH, W. J. MARTIN, D. R. NICHOLS, and F. R. HEILMAN. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **33**, 187–193, April 16, 1958. 7 refs.

At the Mayo Clinic a comparative study was undertaken of the serum concentration of triacetyloleandomycin, a synthetic derivative of oleandomycin, and erythromycin, the bacteriostatic effects of the two sera being also compared. A total of 25 subjects with normal renal function received 500 mg. of erythromycin by mouth every 6 hours to a total of four doses, blood being withdrawn for assay two hours after the last dose. After an interval of 24 hours the subjects were given triacetyloleandomycin in a similar dosage. Serum was assayed by the cup-plate method, the test organism being *Sarcina lutea*. Serum bactericidal tests were carried out with a strain of *Staphylococcus pyogenes* (2891), the endpoint actually being bacteriostatic and not bactericidal because of the impossibility of attaining bactericidal levels with the doses used.

No significant difference was observed between the mean serum concentrations of the two drugs, these (in μg. per ml. of serum $\pm$ the standard error) being 3·32 $\pm$0·35 for triacetyloleandomycin and 3·40$\pm$0·54 for erythromycin. Similarly, the dilutions required for inhibition of bacterial growth *in vitro* were not significantly different, but statistical analysis revealed that the ability of erythromycin to produce "partial bacterial killing" was slightly greater than that of triacetyloleandomycin.

The authors conclude that there is no significant difference between the efficacy *in vitro* of the two drugs, but that erythromycin is probably preferable in the treatment of micrococcal infections sensitive to both drugs. *Gerald Sandler*

1302. **Observations on the Mode of Action of Oleandomycin**
G. L. HOBBY and T. F. LENERT. *Antibiotics and Chemotherapy* [*Antibiot. and Chemother.*] **8**, 219–227, May, 1958. 9 figs., 9 refs.

The action of oleandomycin *in vitro* on two strains of *Staphylococcus aureus*, Strain NHY 235 (antibiotic-susceptible) and Strain 400 (penicillin- and oxytetracycline-resistant), and on a strain of *Streptococcus haemolyticus* has been investigated. The antibiotic may be found to exert either a bactericidal or a bacteriostatic effect, depending on the number of organisms present, the concentration of the drug, and even more on the time at which the observations are made.

Oleandomycin appears to have an almost immediate effect in preventing cell multiplication in susceptible organisms, but like the sulphonamides it causes a decrease in the number of culturable cells within a given population only after 5 to 7 hours contact with the organism. Hence, it is thought, its bactericidal action may be dependent on the gradual depletion of the bacterial stores of some essential metabolite whose formation is inhibited by the action of the drug. The period during which microorganisms are most rapidly destroyed by oleandomycin follows the period during which cell multiplication (in the absence of the drug) occurs most rapidly. This is in contrast to the behaviour of penicillin and other antibiotics. It is generally accepted that the majority of antibiotics are most effective when active multiplication of the microorganism is taking place. The authors conclude that the present observations suggest, but do not establish conclusively, that cell multiplication is also essential for the action of oleandomycin. *L. A. Elson*

1303. **The Chemotherapy of Malaria.** [Review Article]
A. F. CROWTHER. *Journal of Pharmacy and Pharmacology* [*J. Pharm. (Lond.)*] **10**, 337–347, June, 1958. 1 fig., bibliography.

Infectious Diseases

1304. **Acute Psychoses Due to Encephalitis following Asian Influenza**
E. BENTAL. *Lancet* [*Lancet*] **2**, 18–20, July 5, 1958. 5 figs., 10 refs.

During the epidemic of Asian influenza in Jerusalem in 1957 3 children aged 15, 11½, and 9½ years respectively with acute psychosis after influenza were admitted to the Rothschild–Hadassah University Hospital in a state of acute anxiety, confusion, and restlessness, and expressing ideas of persecution. In all 3 cases the electroencephalograms (which are reproduced with the case reports) were diffusely abnormal. All gave high haemagglutination-inhibition titres against the Singapore strain of influenza-A virus. The patients recovered from their psychoses in 6 to 8 days, but the electroencephalograms remained abnormal longer and there was a relapse of the psychotic condition 10 days later in one case. The author concludes that the psychosis in each case was the main or only manifestation of encephalitis following influenza. *G. C. R. Morris*

1305. **Psychosis following Asian Influenza in Barbados**
R. M. L. STILL. *Lancet* [*Lancet*] **2**, 20–21, July 5, 1958.

The author reports that during the 5-week epidemic of Asian influenza in the autumn of 1957 in the West Indies 19 patients, mostly young adults, were admitted to the Mental Hospital, Barbados, with psychoses "definitely attributable" to influenza. Clinical reports of 4 illustrative cases are presented, including those of 2 of 7 patients who had hallucinations of a strange unpleasant smell. All the patients recovered within 4 months, after 15 had been given electric convulsion therapy and 2 of them insulin in addition. No special treatment was given in the other 4 cases. There was no apparent correlation between the occurrence of psychosis and the severity of the influenzal attack. *G. C. R. Morris*

1306. **Severe and Fatal Pneumonia in Infants and Young Children Associated with Adenovirus Infections**
C. CHANY, P. LÉPINE, M. LELONG, LE-TAN-VINH, P. SATGÉ, and J. VIRAT. *American Journal of Hygiene* [*Amer. J. Hyg.*] **67**, 367–378, May, 1958. 5 figs., 17 refs.

During a 15-month period ending in February, 1957, a total of 273 children with "acute viral pneumonia" were admitted to St. Vincent de Paul Hospital, Paris. From the results of intensive investigations the authors considered that in 23 of the cases the pneumonia was caused by an adenovirus infection. For the most part the affected children, aged 6 months to 5 years, were admitted during the winter months. The clinical picture was that of an upper respiratory tract infection followed by pneumonia with the usual physical and radiological signs. Red and swollen eyes were observed in 11 children, a morbilliform rash in 6, meningism in 5, and signs of encephalitis in 4. Unfortunately, 4 of the children died, but most of the remaining 19 were only moderately ill, the acute stage lasting not more than 4 to 5 days. Post-mortem examination revealed marked necrosis in the bronchi and in the lung parenchyma itself. Characteristic and possibly specific inclusion bodies showing a "rosette" pattern were noted and were considered of value in establishing the diagnosis.

In the authors' view the possible very severe nature of these infections raises the question of immunization against the adenoviruses. *John Fry*

1307. **A Clinical Study of the Effects of Nisone (Prednisone) in Laryngeal Diphtheria with Obstruction**
S. A. A. SAMI and R. P. SINHA. *Indian Journal of Pediatrics* [*Indian J. Pediat.*] **25**, 101–106, April [received July], 1958.

A clinical trial was carried out at the Infectious Diseases Hospital, Patna, India, to test the hypothesis that, by virtue of its anti-inflammatory action, prednisone might be able to reduce oedema and spasm in laryngeal diphtheria and that its administration might thus obviate the necessity for tracheotomy. Its use in cases in acute danger of asphyxiation was obviously not practicable, as prednisone given by mouth requires 12 to 18 hours to exert its full clinical effect. The trial was therefore limited to mild and moderately severe cases of diphtheritic laryngeal obstruction, 12 children being treated with 10 to 20 mg. of prednisone daily in addition to the customary routine therapy for diphtheria and the results compared with those in a comparable control group treated without prednisone. There were 6 children with mild and 6 with moderately severe obstruction in each group.

In no case in the group given prednisone had tracheotomy to be performed, whereas 4 tracheotomies were necessary in the control group. There was one death in the prednisone group and 3 in the control group. On the average, clinical improvement started in the prednisone group within 14 hours and in the control group within 41 hours of starting treatment, while the average times taken for all signs of laryngeal obstruction to disappear were 2·5 and 4·5 days respectively. The average stay in hospital of the patients receiving prednisone was 6 days less than that of the control group.

Although the authors regard this account as a preliminary report only and stress the need for trials on a larger scale, their results have made them sufficiently enthusiastic to call their treatment method "medical tracheotomy". *K. Zinnemann*

1308. **Tetanus. A Review of 356 Cases with Special Reference to Treatment with Mephenesin.** [In English]
E. W. ANDERSEN and R. A. NAVARATNE. *Acta anaesthesiologica Scandinavica* [*Acta anaesth. scand.*] **2**, 81–89, 1958. 2 figs., 33 refs.

Tuberculosis

1309. **Experimental Basis of Antituberculous Chemoprophylaxis with Isoniazid.** (Basi sperimentali della chemioprofilassi antitubercolare mediante isoniazide)
M. Lucchesi and G. Spina. *Rivista della tuberculosi e delle malattie dell'apparato respiratorio* [*Riv. Tuberc.*] **6**, 103–130 and 131–147, March–April, 1958. 10 figs., 12 refs.

The authors have performed controlled experiments on guinea-pigs at the Carlo Forlanini Institute, Rome, in order to study certain aspects of isoniazid prophylaxis against tuberculosis. A standard strain of tubercle bacilli, resistant to streptomycin but sensitive to isoniazid, was used to inoculate 182 animals, which were then given 15 mg. of isoniazid per kg. body weight daily for 4 months.

At the end of this period 50 of the animals were given a fresh inoculation of the same strain of tubercle bacilli and treated with isoniazid for a further 4 months. Whereas 28% were tuberculin-positive at the end of the first course of treatment, 80% were tuberculin-positive 5 and 8 months later. In animals killed at intervals during and after treatment there was scanty histological evidence of healing tuberculous lesions, and no tubercle bacilli could be cultured. Another group of 50 were left without further treatment or inoculation after the first 4 months. Seven months later the proportion of tuberculin-positive animals had increased from 50% to 77%. Tubercle bacilli were grown from 15 of the 36 animals killed at various stages, but none of the strains were isoniazid-resistant. [The concentrations of isoniazid used in testing sensitivity are not given.] Macroscopic tuberculous lesions were present in some cases and lymphocytic granulomata and early fibrosis were seen on microscopical examination of the lungs in others. A third group of 50 animals were given a second inoculation of tubercle bacilli, but no more isoniazid. The proportion of tuberculin-positive animals increased from 55·4% to 100% in the next 2 months. From all of 32 animals killed 2 to 3 months after reinfection tubercle bacilli were grown, but again no resistance to isoniazid was found. Widespread acute tuberculous lesions were present in all these animals. A further group of 16 animals which remained tuberculin-negative at the end of their treatment with isoniazid were then given B.C.G., all becoming tuberculin-positive within 2 months. From only one of 13 animals killed 2 to 3 months after B.C.G. vaccination could tubercle bacilli be cultured, and in none were there any gross signs of tuberculosis. A similar and equal group were given Petragnani's *anatuberculina integrale* instead of B.C.G. All became tuberculin-positive, but tubercle bacilli were cultured at necropsy from 4 of the 16, and in several cases tuberculous lesions were seen.

The authors summarize their conclusions from this series of experiments as follows. (1) Guinea-pigs which have been protected against tuberculous infection with isoniazid can be protected again by a second course of the drug. (2) After a protective course of isoniazid animals remain protected for a further 4 months, but are increasingly susceptible thereafter. (3) Animals which remain tuberculin-negative after infection and prophylactic treatment may be protected against further tuberculosis by inoculation with B.C.G. vaccine and, to a lesser extent, with anatuberculin. They warn against the direct application of these conclusions to tuberculosis in man.

From observations made in further experiments on guinea-pigs the authors claim that when B.C.G. and isoniazid are given at the same time and in the presence of a pre-existing infection neither interferes with the protection given by the other. But when there is no existing infection the administration of isoniazid seriously interferes with the protective effect of B.C.G. and with the development of allergy. When animals were vaccinated with B.C.G. and then infected and treated prophylactically with isoniazid, isoniazid-resistant tubercle bacilli were isolated in a large proportion of cases.

Arnold Pines

1310. **Extraperiosteal Plombage in the Treatment of Pulmonary Tuberculosis**
F. H. Young. *Thorax* [*Thorax*] **13**, 130–135, June, 1958. 3 figs., 9 refs.

From the Brompton Hospital, London, comes this report on 66 patients (34 women and 32 men) on whom extraperiosteal plombage was performed 71 times. Careful follow-up for an average period of 5 years (minimum 3 years) showed that 54 patients were well without further operation, 2 died of coronary thrombosis 3 years after the operation (but in these cases the pulmonary disease was found post mortem to be healed), 7 were well after a further operation, one died of progressive pulmonary tuberculosis, one had active pulmonary tuberculosis at the time of follow-up, and one died unexpectedly just after the operation, no complications having been expected. Of 70 of the plombages performed, 62 have been satisfactory; in 2 of the remaining 8 cases the plombage was removed and resection performed for unclosed cavities, in 5 thoracoplasty was later performed because of infection of the space, and in one patient who later died of pulmonary tuberculosis the space was found to be infected.

Of 46 plombages performed after adequate antituberculous drug treatment, subsequent infection of the space developed in only one case (2·5%), whereas of 24 cases in which the drug treatment was considered inadequate, infection of the space occurred in 5 (20%). The author considers that extraperiosteal plombage in a patient who has had adequate chemotherapy is preferable to thoracoplasty, and in some cases in which the disease is extensive and transgresses anatomical boundaries plombage may be preferable to resection. *G. M. Little*

1311. **The Pathology and Bacteriology of Resected Tuberculous Lung Lesions after Chemotherapy**
D. J. COTTER, H. M. FOREMAN, and R. M. E. SEAL. *Thorax* [*Thorax*] **13**, 150–158, June, 1958. 14 figs., 13 refs.

The authors report the results of a pathological and bacteriological study of 240 resected specimens of lung from 218 patients treated with antibiotics for pulmonary tuberculosis at Sully Hospital, Sully, Glamorganshire. A sample of caseous material either from a cavity or from the largest caseous lesion was taken aseptically and cultured for tubercle bacilli. On examination of direct smears in 65% of cases acid-fast bacilli were found, but only in 12% was culture positive. In addition, of 200 guinea-pigs inoculated with caseous material, only 10·7% developed a positive reaction.

" Good chemotherapy " (that is, continuous treatment with antituberculous drugs in adequate dosage for at least 8 months) resulted in the formation of collagenous capsules around the lesions, and a marked reduction in the percentage of lesions positive on culture was correlated with improved chemotherapeutic regimens following the introduction of new antituberculous agents. The percentage of positive findings on direct examination increased in proportion to the size of the lesion, but only one positive culture was obtained in the group of patients receiving " good " chemotherapy. Of 34 patients with resistant organisms in their sputum at some time before resection, 12 (37%) had lesions positive on culture, compared with only 7% of those with fully sensitive organisms. Of the 93 patients with cavities, closure of the cavity was obtained by means of chemotherapy and posture in 80%. The authors attribute this satisfactory closure rate more to correct postural treatment than to the quality of the chemotherapy, since the group of patients receiving the best type of chemotherapy showed the lowest percentage of cavity closure. It is pointed out, however, that many of the cavities in this group were smooth-walled.

G. M. Little

1312. **Aspiration in the Treatment of Primary Tuberculous Pleural Effusion**
S. E. LARGE and R. K. LEVICK. *British Medical Journal* [*Brit. med. J.*] **1**, 1512–1514, June 28, 1958. 8 refs.

A comparative investigation of the results obtained with single and with repeated aspiration in the treatment of 52 patients with primary tuberculous effusion is reported from the Connaught Hospital (Army Chest Centre), Hindhead, Surrey. Routine treatment consisted in rest in bed for 3 months with administration of 200 mg. of isoniazid daily and a total dose over the treatment period of 140 to 150 g. of streptomycin. Patients who still had pyrexia or a raised erythrocyte sedimentation rate (E.S.R.) at the end of this period continued to rest in bed until these had subsided. Upgrading took a further 3 months. In all cases breathing exercises were started when the temperature became normal. Of the 52 patients, 19 were subjected to a single aspiration of not more than 100 ml. and 33 to repeated aspiration (average number 4·2 per patient). In the latter 1 g. streptomycin in 10 ml. water was instilled into the pleural cavity after each aspiration. The mean duration of pyrexia was slightly shortened and that of raised E.S.R. slightly prolonged by repeated aspiration. In the early stages clearing was more rapid in this group, but at 6 months there was no significant difference between the two groups in the amount of pleural opacity.

I. Ansell

1313. **Respiratory Inadequacy after Thoracic Surgery in Tuberculous Patients**
A. H. B. MASSON and J. D. ROBERTSON. *British Medical Journal* [*Brit. med. J.*] **1**, 1516–1518, June 28, 1958. 5 refs.

The factors which adversely affect respiratory function after thoracic operations include infection, paradoxical respiration after thoracoplasty, atelectasis, compression of the lung by air or fluid, pulmonary congestion, reduction in functioning lung tissue by disease or resection, wound pain, and drugs, particularly analgesics and sedatives. In this paper from the Royal Infirmary, Edinburgh, a method of treating respiratory inadequacy by tracheostomy and intermittent positive-pressure respiration is described. Tracheostomy was performed through the second and third tracheal rings. A shortened endotracheal tube fitted with a Magill T-piece was inserted into the trachea, the cuff inflated, and connexion made to an intermittent positive-pressure respirator. Secretions were aspirated at frequent intervals through a shortened Tiemann's catheter. The authors describe 5 cases in detail. In 4 of the patients, 3 of whom had been subjected to thoracoplasty, respiratory paradox was an important factor and the pneumomatic respirator was required for as long as 3 weeks until the chest wall was firmly healed.

I. Ansell

1314. **On the Effectiveness of Marsilid (INPH) in Bone and Joint Tuberculosis**
R. KATAYAMA, A. TAKAYAMA, T. ISHIZUKA, J. SATO, T. OHTO, K. MIYOSHI, I. KOIZUMI, and J. INOUE, *Sea View Hospital Bulletin* [*Sea View Hosp. Bull.*] **17**, 6–16, Jan. [received June], 1958. 10 refs.

At the Tokyo Jikei-Kai School of Medicine iproniazid was given in a dosage of 3 mg. per kg. body weight to 3 patients with vertebral caries with abscess. The effect of the drug was assessed on the basis of the amount of pus in the cold abscess, the specific gravity of the pus, and the percentage of solids it contained. *Mycobacterium tuberculosis* was isolated from the pus in the early stages of treatment in all 3 cases; later the bacterial count decreased sharply until, after 8 weeks' treatment, cultures were negative.

Tuberculosis of the knee was induced in 4 groups of 25 healthy guinea-pigs, 3 groups being treated respectively with iproniazid, streptomycin, and isoniazid and one group serving as a control. Iproniazid was found to be as effective as streptomycin or isoniazid. Iproniazid-resistant tubercle bacilli injected into healthy guinea-pigs appeared to be less virulent than non-resistant organisms.

[At higher dosage levels iproniazid has been shown to exert a toxic effect on the central nervous system.]

Peter Ring

Venereal Diseases

1315. **Certain Aspects of So-called Serological Syphilis in Military Personnel.** (Quelques aspects de la syphilis dite sérologique, en milieu militaire)
E. Reboul, L. Olivier, and J. Bediez. *Revue d'hygiène et de médecine sociale* [*Rev. Hyg. Méd. soc.*] **6**, 261–274, April–May, 1958.

Latent syphilis, which has lately assumed a position of increasing importance, has been the subject of much confused observation and thinking; in the authors' opinion it would be more exactly termed "syphilis diagnosed solely by serological tests". The present study, reported from the Hôpital Militaire Desgenettes, Lyons, has the merit that all the patients were studied between 1951 and 1955 by the same observer and the serological tests all performed in one laboratory with the same technique and reagents. Further, the patients were examined repeatedly and meticulously in order to exclude any with clinical signs of syphilis. The standard serological tests employed included the Wassermann, Kolmer, and Kline tests, and the treponemal immobilization (T.P.I.) test was used to confirm the presence of syphilis or to exclude false positive reactions, which were found in 50 cases. Of the total of 233 cases of syphilis seen in the 5-year period, 71 ran the recognized clinical course, but 162 showed no clinical signs and the diagnosis was based on serological tests alone. Of the latter the T.P.I. test gave a positive result in 135 and doubtful in 7; it was not performed in 20 cases. Only the 135 patients with a frankly positive T.P.I. reaction are considered in this study.

The proportion of those diagnosed solely on the serological findings to the total number of cases, that is, 135 out of 206, is interesting, since in the 5-year period 1946–50 the proportion of latent to clinical syphilis was 27 cases out of 185. There has therefore been both a relative and an absolute increase in latent (serological positive) syphilis. The majority of the patients were young recruits in the age group 19 to 25 years, with some older men aged 25 to 55. A high proportion (90) were Europeans and the most important factor in their history was overseas service. Previous treatment with antibiotics, likely to render syphilis latent, had been given in only a small number of cases (9 out of 83). The results of treatment were known in 75 of 135 cases; the serology became negative in 21 (28%), showed improvement in 27 (30%), no change in 26 (34·6%), and further deterioration in 1 (1·3%). The vital factor in improvement appeared to be the duration of syphilis before treatment was started, which in most cases consisted of 15 mega units of penicillin plus 15 injections of bismuth.

The authors discuss the possibility of the existence of a type of syphilis which is devoid of clinical signs and which is associated with the decline in severity of the disease that has gradually occurred over a long period of time. In conclusion they reiterate their opinion that latent syphilis is becoming both relatively and absolutely more common. *Robert Lees*

1316. **Electroencephalography in the Evaluation of the Course of Treated Syphilis and Neurosyphilis.** (Значение электроэнцефалографии для оценки течения и лечения сифилиса и нейросифилиса)
P. Ja. Malykin, A. I. Sokolin, and T. V. Vasil'ev. *Вестник Дерматологии и Венерологии* [*Vestn. Derm. Vener.*] **32**, 36–46, No. 2, March–April, 1958. 9 figs., 8 refs.

Since 1952 at the Central Institute of Dermatology and Venereology, Moscow, the electroencephalogram (EEG) has been recorded in 234 patients, of whom 140 had early seronegative syphilis, 27 latent syphilis, 7 tertiary gummata, and 69 neurosyphilis, recordings being made before, during, and after treatment. In those with seronegative primary syphilis the EEG was almost normal. In patients with seropositive primary syphilis, however, there were frequent changes of rhythm with prevalence of slow waves, but seldom real disorganization of the rhythm. Slow rhythms, sometimes with complete disappearance of "bio-potentials", were also observed in cases of late cerebral and cerebrospinal forms of the disease. Fast rhythms were a characteristic finding in cases of secondary syphilis (being more pronounced in recurrent cases than in early secondary cases), tertiary syphilis, tabes, and early forms of latent meningitis.

It was noted that treatment with antibiotics often improved the EEG or even restored it to normal, whereas treatment with arsenical preparations caused initial deterioration, improvement resulting only after the 5th or 6th injection, with consequent delay in the return of the EEG to normal. The authors also found the EEG a useful guide in deciding whether to administer sedatives or stimulants. *H. Makowska*

1317. **The Treponemal Complement-fixation Tests in Probable Latent Syphilis or Biologic False Positive Reactions**
A. H. Wheeler, E. M. Brandon, and A. C. Curtis. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **30**, 265–268, May, 1958. 7 refs.

At the University Hospital, Ann Arbor, Michigan, the treponemal immobilization (T.P.I.) test was carried out in parallel with the treponemal complement-fixation (T.P.C.F.) test described by Portnoy and Magnuson (*J. Immunol.*, 1955, **75**, 348; *Abstr. Wld Med.*, 1956, **19**, 442) on 394 sera from patients whose reaction to standard serological tests for syphilis (S.T.S.) had been positive, but in whom the diagnosis of syphilis was questionable on clinical grounds. The T.P.I. test was found to be

slightly the more sensitive, giving 52% of positive results compared with 48% with the T.P.C.F. test. The results of the two tests agreed in 92% of cases. In tests on a further group of 127 patients with a tentative clinical diagnosis of syphilis the T.P.I. reaction was positive in 77 cases and the T.P.C.F. reaction in 69. Another group of 108 sera gave positive STS reactions which were thought to be non-specific; the T.P.I. reaction was found to be negative in 68 of these and the T.P.C.F. reaction in 75.

The reproducibility of the T.P.C.F. reaction was then examined by testing 88 sera in duplicate with two different batches of standardized T.P.C.F. antigen. The same results were obtained with the two antigens in 82 cases, but in the remaining 6 the results differed, being doubtful and negative respectively in 3 cases, 4+ and negative in one, and 4+ and 1+ in 2. When duplicate tests were performed on aliquots of 61 sera on different days, but using the same batch of antigen for both, there was disagreement in 3 cases, in all of which the result of one test was doubtful and of the other negative.

Some preliminary studies were carried out with the Reiter protein antigen in complement-fixation tests. This was found to be considerably more active than the T.P.C.F. antigen, having a titre of 1,280 when two batches of the T.P.C.F. antigen had titres of 20 and 40 respectively against the same serum in 1:40 dilution. The results of comparative tests on a small number of sera are described and suggest that in spite of the apparent similarity of different batches of standardized T.P.C.F. antigen there may be differences between them which can be detected only by parallel tests against individual weakly reactive sera. It is recommended that these be performed in addition to the conventional checkerboard titration with pooled positive and negative sera. *A. E. Wilkinson*

GONORRHOEA

1318. **Sensitivity of Strains of Gonococci to Penicillin, Sulphathiazole, and Streptomycin**

J. E. CRADOCK-WATSON, R. A. SHOOTER, and C. S. NICOL. *British Medical Journal* [*Brit. med. J.*] **1**, 1091–1092, May 10, 1958. 9 refs.

A total of 211 strains of gonococci obtained from 190 male and 10 female patients attending St. Bartholomew's and St. Thomas's Hospitals, London, were tested for sensitivity to penicillin, streptomycin, and sulphathiazole. The technique of isolation and testing and the control measures adopted are described. Sensitivity was determined by culture on chocolate agar plates containing serial dilutions of the drugs tested, the plates being incubated in candle-jars for 48 hours.

The minimum inhibitory concentration of penicillin was 0·064 unit or less per ml. for 162 of the strains tested, 0·128 unit per ml. for 17, 0·256 unit per ml. for 16, and 0·512 unit per ml. for 5. For 158 strains the minimum inhibitory concentration of streptomycin was 4 μg. or less per ml. and for the remaining 42 tested it was 16 μg. per ml. All but one of 200 strains were sensitive to 8 mg. or less of sulphathiazole per 100 ml.

At both hospitals the routine treatment was with a single injection of 3,000,000 units of procaine penicillin. Recurrence occurred in 25 cases. Penicillin-resistant strains (that is, strains needing 0·128 unit or more per ml. for inhibition) were isolated from 38 patients, of whom 13 had a recurrence, whereas only 12 recurrences were seen among the remaining 162 patients. In 10 of the 25 cases of recurrence further sensitivity tests were performed. From 7 of these patients, at least 6 of whom were thought to be suffering from relapse rather than reinfection, the original resistant strain was again isolated. In one of the remaining cases a resistant strain had been replaced by a sensitive one, reinfection being probable, and in 2 both strains were sensitive.

The literature concerning the incidence of penicillin resistance in gonococci is reviewed and the authors contrast their findings with the lack of evidence from other sources that penicillin-resistant strains are emerging. They intend in future to use 6,000,000 units of penicillin for primary treatment and to treat clinical relapses with streptomycin and sulphonamides. *F. Hillman*

1319. **Oral Penicillin for Gonorrhoea. Some Experiences with Phenoxymethyl Penicillin (Penicillin V) in White and Negro Patients**

R. R. WILLCOX. *British Journal of Venereal Diseases* [*Brit. J. vener. Dis.*] **34**, 118–121, June, 1958. 11 refs.

It has been shown by previous workers that penicillin given by mouth and in relatively high dosage achieves cure in cases of gonorrhoea, but that the results are much less certain than those following parenteral administration of the antibiotic. In an attempt to find a satisfactory method of oral treatment of acute gonorrhoea, the author, at St. Mary's Hospital, London, tried phenoxymethylpenicillin, a total of 85 patients, 33 of whom were white, receiving 2 to 3 mega units by mouth either in one dose or in two.

Of the 33 white patients, 27 were followed up for periods varying from a few days to 3 months; during this time there were no definite relapses and the percentage of reinfections was 14·8. The results in this group were considered to be as good as those obtained with injections and no material difference was noted whether total dosage was 2 or 3 mega units or whether it was administered in one or 2 doses. Of the 52 coloured patients, 49 were followed up for similar periods. In this group the percentage of reinfections was 12·2 and of suspected failures 28·6; the best results were obtained with a single dose of 3 mega units.

The results show well-marked racial differences, those in coloured patients being poor, while those in white patients were comparable with the results obtained with 600,000 units of procaine penicillin given parenterally. The author considers that this striking racial difference in response may be due in part to differences in the social behaviour of white and coloured people, and in part to increased penicillin resistance of the organism in its passage through the relatively "closed" community of the consorts of coloured patients. The importance of separate evaluation of results according to race is emphasized. *A. J. Gill*

Tropical Medicine

1320. **Sickle Cell Haemoglobin C Disease and Homozygous Haemoglobin C Disease in Nigerian Children**
R. G. HENDRICKSE. *West African Medical Journal* [*W. Afr. med. J.*] 7, 80–90, June, 1958. 36 refs.

Although inherited abnormalities of the haemoglobin molecule due to sickle-cell and haemoglobin-C genes are common in West Africa, yet there have been few reports of their occurrence in combination. The author, writing from University College Hospital, Ibadan, Nigeria, summarizes the clinical findings in 8 cases of sickle-cell–haemoglobin-C disease seen in Nigerian children, describing 3 cases in detail.

The average age at diagnosis was 6 years, with a range of 4 months to 9 years. The commonest presenting symptom was pain in the limbs or abdomen in 7 cases, in 3 of which the pain was associated with tender swellings of joints and in one with swelling over bone, though none showed radiological evidence of bone disease. Other presenting symptoms included fever (5 cases), anorexia (2), vomiting (2), jaundice (2), and haematuria (one). Splenomegaly was noted in 6 cases, but this was much less marked than that seen in children with sickle-cell anaemia. Haemoglobin levels were generally within the range found in healthy Nigerian children, but in 2 cases fell during a crisis and returned to normal level without treatment by transfusion or haematinics. Erythrocyte sickling could be induced in all cases, and in 5 or 6 patients tested there was decreased osmotic fragility of the erythrocytes. Target cells were a prominent feature in stained blood films, while leucocyte counts varied between 10,000 and 20,000 per c.mm. Filter-paper electrophoresis of the haemoglobin showed only haemoglobins S and C in every case. Crises were milder and less frequent than in sickle-cell anaemia, though in 2 cases a crisis was associated with severe illness. There were no deaths, and during remissions the patients appeared to be in normal health. The author found antibiotics beneficial in episodes of limb pain and swelling, but no curative treatment is known.

One case of homozygous haemoglobin-C disease in a 6-year-old Nigerian child is described in detail and the findings in 11 previously reported cases are given for comparison. Attention is drawn to the invariable finding of target cells. Although these cells may also be found in other conditions, such as thallassaemia, sickle-cell anaemia, and cirrhosis, their presence in large numbers in a patient in West Africa "should put one in mind of disease associated with haemoglobin C". The clinical manifestations of the sickling disorders are usually attributed to the consequences of intravascular sickling. The relative mildness of sickle-cell–haemoglobin-C disease as compared with sickle-cell anaemia is explained by the fact that in the former condition only half (instead of almost all) the haemoglobin is of the S type. However, the occurrence of periodic episodes of arthralgia and abdominal pain in homozygous haemoglobin-C disease, in which sickling does not occur, suggests that "these manifestations in sickle cell disease may involve mechanisms other than simple intravascular sickling". *I. Berkinshaw-Smith*

1321. **Incidence, Aetiology, and Prevention of Heat Illness on Ships in the Persian Gulf**
C. S. LEITHEAD, J. GUTHRIE, S. DE LA PLACE, and B. MAEGRAITH. *Lancet* [*Lancet*] 2, 109–115, July 19, 1958. 2 figs., bibliography.

A vast international fleet of oil-tankers now sails in the Persian Gulf, and heat illness aboard the ships is a serious problem. 128 such cases seen at one port in the summer of 1956 and 1957 are reported, among which were 3 cases of heat hyperpyrexia (1 fatal), 5 of borderline heat hyperpyrexia, 59 of salt-deficiency heat exhaustion, 1 of anhidrotic heat exhaustion, and 60 of minor heat syndromes (unclassified). A large proportion of these cases occurred in the month of August each year. Tanker crews going to the Persian Gulf are exposed to heat especially in the 10 days after they leave the Suez Canal. During this period they have to become rapidly acclimatized, or regain the acclimatization lost after their previous voyage. The additional heat-stress of engine-rooms and galleys accounted for over half the cases.

If heat illness is to be prevented aboard such vessels, responsible officers must have fuller understanding of the risks. Crews must be induced to take supplementary salt in quantities sufficient to replace what they lose in sweat; and officers must be readier to limit activity before it becomes dangerous. For saving lives and safeguarding health these personal preventive measures are almost as necessary as maximum air-conditioning of the ships.—[Authors' summary.]

[The 128 cases constituted about 1 in 850 of the subjects at risk, with higher incidence among the engine-room and galley crews than among men working on deck.—EDITOR.]

1322. **Tuberculin and Lepromin Sensitivity in E. Nigeria**
T. F. DAVEY, S. E. DREWETT, and C. STONE. *Leprosy Review* [*Leprosy Rev.*] 29, 81–101, April, 1958. 7 figs., 16 refs.

The relationship between sensitivity to tuberculin and lepromin has been studied by the Nigeria Leprosy Service Research Unit, Uzuakoli. Tuberculin and lepromin sensitivity tests were carried out simultaneously on: (1) 3,000 school-children in one urban area and five rural areas; and (2) the complete population (2,500 subjects) of four villages. Tuberculin sensitivity was high in the urban area and was lower in the rural areas. Sensitivity to lepromin and to tuberculin tended to occur in association in the same subjects. In the urban area it appeared possible that tuberculosis was contributing to lepromin

sensitivity, but no evidence of this was found. In adults sensitivity to lepromin and to tuberculin attained stable levels, and then the association between the two largely disappeared. The authors consider it improbable that contact with *Mycobacterium leprae* could alone be responsible for the different levels of lepromin sensitivity observed. Non-specific geographical and constitutiona factors appeared to have a great influence, and it is suggested that these are responsible for the association between tuberculin and lepromin sensitivity in Eastern Nigeria.

[This paper contains many statistics and the original should be consulted by those interested.]

F. Hawking

1323. **New Synthetic Compounds in the Treatment of Amoebiasis**

A. K. R. Chowdhury, Amiya K. R. Chowdhury, and R. Nandi. *Journal of the Indian Medical Association* [*J. Indian med. Ass.*] **30**, 239–251, April 16, 1958. 1 ref.

The effect of two new synthetic drugs was determined on a series of patients at the R.G. Kar Medical College Hospital, Calcutta, suffering from amoebic dysentery. These were: (1) 5:6-quinone-4:7-phenanthroline semicarbazone (11/925); and (2) 5:6-quinone-4:7-phenanthroline (11/925C). They were administered orally, one or 2 (rarely 4) stool examinations being carried out after treatment.

The dose of 11/925 was 600 mg. per day for 7 to 10 days in acute cases and 300 to 500 mg. per day in chronic cases. Out of 21 cases treated with this drug, clinical cure was obtained in 12, some improvement in 5, and no benefit in 4 cases. There was a high incidence (18 cases) of side-effects, chiefly in the form of nausea and vomiting. Drug 11/925C was administered in a dosage of 300 to 500 mg. per day for 7 to 10 days to 40 patients. Clinical cure was observed in 30, some beneficial effect in 9, and no effect in 1 case. This drug produced no side-effects, though highly coloured urine was observed in some cases.

[This paper does not describe the effect of these drugs on *Entamoeba histolytica*, but on the clinical manifestations of infection with this parasite.] *R. A. Neal*

1324. **Clinical Trial with Two New Synthetic Compounds in Amoebiasis**

P. K. Chatterjee, S. Mukherjee, S. Ghose, K. P. Datta, and S. Sircar. *Journal of the Indian Medical Association* [*J. Indian med. Ass.*] **30**, 251–254, April 16, 1958. 2 refs.

At the National Medical College Hospital, Calcutta, the two new synthetic drugs 5:6-quinone-4:7-phenanthroline semicarbazone (11/925) and 5:6-quinone-4:7-phenanthroline (11/925C) were administered respectively to 34 and 13 hospital patients infected with *Entamoeba histolytica*.

At first the drugs were given in a dosage of 600 mg. per day for 10 days, but this had to be reduced to 300 mg. in the case of 11/925 owing to undesirable side-effects. The stools were examined " periodically during the course of treatment and afterwards ". Of 7 patients with amoebae in the faeces before treatment with 11/925, all were freed from *E. histolytica*, but only 5 out of 7 similar cases given 11/925C were cured. Of 18 cases in which cysts of *E. histolytica* were found in the faeces before treatment, 16 were freed after treatment with 11/925, whereas 11/925C eliminated the parasite in only 5 out of 9 similar cases. The authors consider the semicarbazone derivative to be the more effective amoebicide, but it causes unpleasant side-effects.

[Further details of the number and frequency of microscopical faecal examinations after treatment are necessary for the reader to obtain a reliable estimate of the amoebicidal properties of these drugs.] *R. A. Neal*

1325. **The Treatment of Eosinophilic Lung (Tropical Eosinophilia) with Diethylcarbamazine**

T. J. Danaraj. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **27**, 243–263, April, 1958. 7 figs., bibliography.

Since 1956 at the General Hospital, Singapore, 110 consecutive patients suffering from eosinophilic lung have been treated with diethylcarbamazine. The majority of the patients (101 male and 9 female) were adult Indians. Filariasis, past or present, was excluded on examination of the blood; the sputum did not contain larvae and the stools were free from the eggs of helminths, although in a few instances roundworms or hookworms were present. The symptoms included paroxysmal cough with scanty sputum, thoracic constriction, and occasional asthmatic attacks. The essential features were an eosinophilic leucocytosis, the count exceeding 3,000 per c.mm., streaking and mottling of the lungs on *x*-ray examination, and a raised erythrocyte sedimentation rate (E.S.R.). The dosages of diethylcarbamazine were: 4 mg. per kg. body weight 3 times a day for 4 days (46 patients); 6 mg. per kg. 3 times a day for 5 days (57 patients); and 10 mg. per kg. 3 times a day for 5 days (7 patients). The patients were followed up for periods varying up to 14 months.

Clinical improvement was noted within 4 days; about half the patients were free from symptoms in 7 days and all but one in 4 weeks from the start of treatment. The abnormal signs in the chest had usually cleared by the seventh day. The eosinophil count fell rapidly during the first 5 days and then more slowly: 30 days after the start of treatment the eosinophil count was below 3,000 per c.mm. in all except 6 patients. The E.S.R. fell more gradually and was still raised at the end of the follow-up period in 25 patients. The mottling seen in the chest radiographs cleared by the fourth week, but the streaking persisted longer. Toxic effects, which included vertigo and vomiting, were experienced by 12 patients, 10 of whom were taking the larger doses of the drug. The condition relapsed in 3 patients but responded to a second course of diethylcarbamazine. Only one patient failed to respond to treatment.

The author considers that diethylcarbamazine is a safe and satisfactory drug for the treatment of eosinophilic lung, possibly acting more quickly than the organic arsenicals and certainly being less toxic. He recommends a dosage of 6 mg. per kg. body weight 3 times a day for 5 days. *Arthur Willcox*

Allergy

1326. **Hydroxyzine (Atarax) in Chronic Urticaria and in Allergic Manifestations. Clinical Observations in Man and Experimental Studies on Asthma in Guinea Pigs Produced by Several Agents**
A. R. FEINBERG, J. J. PRUZANSKY, S. M. FEINBERG, and E. W. FISHERMAN. *Journal of Allergy* [*J. Allergy*] **29**, 358–361, July, 1958.

A chance observation led to the investigation at the Northwestern University Medical School, Chicago, of hydroxyzine, a tranquillizer, which in doses of 10 to 25 mg. was found to give complete relief in 15 out of 17 cases of chronic urticaria and partial relief in the other 2. In several of these cases, however, the drug lost its effect after a few weeks, whereas in others the beneficial effect was maintained indefinitely with doses of 10 mg. daily, or even every second or third day. In contrast, tripelennamine gave relief from itching, though only for a few hours, but did not influence the weals, while the results with other tranquillizers were less convincing. In patients with acute urticaria, atopic dermatitis, hay fever, and vasomotor rhinitis hydroxyzine had no constant effect.

In studies on guinea-pigs which were passively sensitized to egg albumen and challenged by exposure to an egg-albumen aerosol, hydroxyzine in a dose of 10 mg. per kg. body weight was completely effective as a protection against anaphylactic shock and almost as effective against aerosols of histamine and serotonin, although less so against acetylcholine. Two antihistaminics administered for comparison had similar protective effects, although in much lower dosage. It is suggested that the sedative action of hydroxyzine is not responsible for its beneficial effect in chronic urticaria and that this effect may be produced through another mediating mechanism apart from its antihistamine, anti-serotonin, and anti-acetylcholine activity.

[It should be remembered that in chronic urticaria, as opposed to acute urticaria, an allergic cause usually cannot be detected.] *H. Herxheimer*

1327. **Basophil Leucocytes in Urticaria, Asthma and Atopic Dermatitis.** [In English]
H. RORSMAN. *Acta allergologica* [*Acta allerg.* (*Kbh.*)] **12**, 205–208, 1958. 19 refs.

In this paper from the University of Lund, Sweden, the author reports an investigation of the number of basophil leucocytes in the blood of patients with urticaria, asthma, or atopic dermatitis. Basophil leucocytes were stained metachromatically with an alcoholic diluting fluid containing toluidine blue, haemolysis being then obtained by the addition of saponin. The cells were counted in a Jessen chamber. A marked decrease in the number of basophil leucocytes was observed in most cases of urticaria, but not in asthma or atopic dermatitis. In 3 patients with cold urticaria and a normal basophil count the blood histamine level was normal or high. A normal basophil count was also found in cases of dermographism and emotional urticaria. *A. W. Frankland*

1328. **Food Allergy in Theory and Practice.** [In English]
K. WILKEN-JENSEN. *Acta allergologica* [*Acta allerg.* (*Kbh.*)] **12**, 142–152, 1958. 21 refs.

In this paper from Rigshospitalet, Copenhagen, the author discusses the difficulties encountered in diagnosing food allergy and detecting the particular allergens concerned, and then describes his own experience. The foodstuffs giving rise to symptoms of allergy may be determined in two ways: (1) by eliminating from the diet for some days or weeks all foods giving a positive reaction to a prick or intracutaneous test, as well as suspected foods, and then allowing the patient to eat a large quantity of each test food for 3 days at a time; (2) by giving one of two specific diets, both of which exclude milk and all its products and eggs, while one excludes in addition all kinds of flour and cereal and the other all fruits and spices. The author used the first of these methods on 63 patients, 38 of whom had symptoms provoked by more than one allergen. The foods most commonly causing symptoms of allergy are listed in a table, the main ones being milk, butter, cheese, and eggs. The author points out that the history is important in the original evaluation of the allergens possibly responsible for symptoms, but even so, dairy products, meat, and flour are rarely suspected from the history. In over two-thirds of the cases in this series a positive reaction was obtained to a combination of the prick and intracutaneous tests. Skin tests for vegetables were not carried out.
A. W. Frankland

1329. **Food Allergy in Children with Asthma and Eczema.** [In English]
V. LEHMUS and K. ROINE. *Acta allergologica* [*Acta allerg.* (*Kbh.*)] **12**, 186–198, 1958. 2 figs., 29 refs.

During the period 1947–56 a total of 1,076 children under 15 years of age suffering from eczema with and without asthma were admitted to the Hospital for Allergic Diseases, Helsinki, and in this paper a study is reported of the results of skin tests, of the leucopenic index (386 cases) and of the general and local reactions to provocation tests. All the patients were tested intracutaneously with various foods, and it was found that the foods mainly responsible for symptoms were cocoa, eggs, milk, wheat, and codfish in that order. Positive skin reactions to foods were more frequent in children with asthma and eczema than in children with asthma alone. In 182 patients (17%) food allergy was considered to be of clinical importance and they were hyposensitized, 158 of them to milk. *A. W. Frankland*

Nutrition and Metabolism

1330. **Congenital and Acquired Agammaglobulinaemia. A Report of Four Cases**
B. G. FIRKIN and C. R. B. BLACKBURN. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **27**, 187–205, April, 1958. 7 figs., bibliography.

The authors describe 4 cases of agammaglobulinaemia seen at the Royal Prince Alfred Hospital, Sydney. Of 2 boys aged 14 years who had had multiple infections, one died suddenly after an anti-cholera injection and the other had splenomegaly, leucopenia, and leg ulcers. The remaining 2 patients were men; one, aged 53 years. had multiple myelomatosis but had not suffered from infections, and the other, aged 23 years, had follicular lymphoblastoma.

In all 4 cases the serum was examined by paper and moving-boundary electrophoresis. In 3 cases no gamma-globulin was detected in the serum, while in the fourth case the gamma-globulin level was much reduced. Immunological studies were carried out on the sera, Ouchterlony's gel-diffusion method being used with a rabbit anti-human-gamma-globulin serum, which was shown to be specific for human gamma globulin. In all 4 cases and one further case of congenital agammaglobulinaemia the serum was found to contain immunologically demonstrable amounts of gamma globulin.

The authors discuss at some length a " working classification " of agammaglobulinaemia and examine many aspects of the problems of resistance and immunity.

Charles Rolland

1331. **Intestinal Absorption of Iodine^{131}-labeled Triolein and Oleic Acid in Normal Subjects and in Steatorrhea**
E. KAPLAN, B. D. EDIDIN, R. C. FRUIN, and L. A. BAKER. *Gastroenterology* [*Gastroenterology*] **34**, 901–909, May, 1958. 6 figs., 11 refs.

At the Veterans Administration Hospital, Hines, Illinois, 4 or 10 ml. of triolein labelled with 30 μc. of radioactive iodine (^{131}I) in 250 ml. of milk was given to 33 male patients without gastro-intestinal disease and the radioactivity in whole blood determined at timed intervals thereafter. A similar test was performed on a further 11 similar patients, using ^{131}I-labelled oleic acid. To both groups Lugol's iodine was administered on the day before the test. The maximum value of radioactivity was reached in 4 to 5 hours with triolein and 3 to 5 hours with oleic acid, and was about 2% in each case.

The test gave normal results with oleic acid in 3 patients with steatorrhoea due to chronic pancreatitis and one steatorrhoeic patient with occlusion of the duodenum distal to the sphincter of Oddi, who received the dose via a jejunostomy. However, the peak value following administration of labelled triolein was reached in these patients in 7 hours and was less than 0·73%. Triolein absorption was improved by administration of pancreatin, but did not reach normal values. In one patient with steatorrhoea due to the malabsorption syndrome both tests showed depressed absorption of fat. Pancreatin had no effect on the absorption of oleic acid, but after 4 days of treatment with cortisone there was a clinical remission of the steatorrhoea and the fat absorption curve returned to normal. The authors suggest, as a screening test, determining the radioactivity in a blood sample 4 hours after giving triolein. If this value is low the test is repeated with oleic acid several days later. In this way, they believe, pancreatic steatorrhoea could be distinguished from idiopathic steatorrhoea.

[This conclusion is hardly justified on the evidence provided by the small number of cases studied.]

M. Lubran

1332. **Some Aspects of the Relation of Ceruloplasmin to Wilson's Disease**
I. H. SCHEINBERG, R. S. HARRIS, A. G. MORELL, and D. DUBIN. *Neurology* [*Neurology* (*Minneap.*)] **8**, 44–51, April, 1958. 3 figs., 14 refs.

A study is reported of the plasma concentration of ceruloplasmin in healthy subjects, in patients with Wilson's disease and unaffected members of their families, and in patients with liver disease or neurological disorders. It was found that the average plasma ceruloplasmin concentration estimated spectrophotometrically was 24 mg. (range 16 to 33 mg.) per 100 ml. in 21 healthy subjects, and 5 mg. (range 0 to 14 mg.) per 100 ml. in 26 patients with Wilson's disease. This difference was highly significant. The half-life of ceruloplasmin was determined in 3 patients with Wilson's disease after incomplete exchange transfusion of enough normal blood to raise the ceruloplasmin concentrations to convenient levels; it was found to be between 3 and 5 days. This is interpreted as lending support to the hypothesis that the essential defect in Wilson's disease is a failure of synthesis rather than an excessive rate of breakdown of ceruloplasmin. If there had been an increased rate of destruction in these cases, then the half-life of ceruloplasmin in healthy individuals would have to be about 400 days in order to account for the differences in plasma concentrations, and this is so much greater than that for other plasma proteins for which determinations are available as to make it intrinsically unlikely.

The plasma ceruloplasmin concentration was not diminished in patients with liver disease, schizophrenia, or a variety of other neurological disorders. The mean ceruloplasmin concentration in 18 parents of patients with Wilson's disease was about 23 mg. (range 12 to 44 mg.) per 100 ml.

H. Harris

1333. **Diagnostic Methods in Intestinal Malabsorption.** [Review Article]
F. M. HUNTER and A. L. PREVATT. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*], **236**, 81–100, July, 1958. Bibliography.

Gastroenterology

1334. **Mucosal Folds at the Cardia as a Component of the Gastro-oesophageal Closing Mechanism**
G. S. MULLER BOTHA. *British Journal of Surgery* [*Brit. J. Surg.*] **45**, 569–580, May, 1958. 24 figs., 8 refs.

It was suggested by Magendie in 1815 that closure at he gastro-oesophageal junction was effected by occlusion of the cardia by a mucosal fold, but no conclusive evidence of the existence of such a fold has ever been put forward. In an investigation carried out at the University of Birmingham the diaphragm, lower oesophagus, stomach, aorta, and surrounding tissues were carefully removed *en bloc* at necropsy [at an unstated interval after death] from 30 adults (aged 18 to 80) and 115 infants and children (aged 32 weeks to 8 years), fixed in formol saline, and examined macroscopically and histologically. No conspicuous mucosal folds were found in the majority of the specimens, though there was very marked variation in the pattern; however, in one or two cases a perfect watertight mucosal seal was found at the cardia. These observations suggested that at least in some persons there is a definite arrangement of special folds, and on the assumption that these may disappear after death careful palpation was carried out on 12 patients at partial gastrectomy under general anaesthesia with relaxants. In every case there was evidence of occluding folds, though hardly any two presented the same pattern. On 2 occasions apposition was so perfect that the orifice was only found after some search—in one case passage of a Ryle's tube was necessary. The tone of the folds appeared to change after some manipulation, and the importance of gentleness in detecting their presence by palpation is emphasized. Sometimes the cushion-like pads lost all resistance, the folds smoothed out, and the orifice became wide open and lax, totally different from its previous state. The cardia was more patulous and the folds less pronounced when a Ryle's tube had been passed before operation. (Such a tube was pulled up before beginning the investigation.)

The pattern of mucosal folds at the gastro-oesophageal junction was then studied in 21 different species post mortem and in 13 of them at operation under the lightest plane of anaesthesia with intravenous or intraperitoneal pentobarbitone or bromethol, the use of relaxants, atropine, or opiates being avoided. Sometimes the changes in fold pattern were too rapid to be followed by the eye, and in 10 species they were studied by means of slow-motion cinematography. In not one instance was there a passive arrangement of folds—they were always controlled and activated by some inherent tone and, at any rate in the dog, variations in pattern seemed to depend on alterations in tone of the surrounding muscle.

The author concludes that mucosal folds are present at the human gastro-oesophageal junction during life and "are normally in close apposition at the cardiac orifice and effect a watertight seal from below". As a result of previous manometric and cineradiographic studies he regards the evidence of the existence of a physiological sphincter at the lower end of the oesophagus as overwhelming, and since "the folds alone are too weak to withstand any substantial strain" this sphincter must draw the folds together so that the final closure may be made by the muscularis mucosae. The internal sphincter acting by itself "will always leave a small conical space where the oesophagus joins the stomach, readily detectable radiologically, and a constant invitation to reflux during sudden sharp rises of intra-abdominal pressure. The pads of mucosa fill this potential space and close the cardiac orifice flush, so that the pressure is dissipated evenly along the stomach wall." He considers that "the idea of a mechanical valve or flap is illogical".

[This important paper should be studied in the original. The abstracter finds it difficult to accept the polemical conclusion. In routine barium-meal work competence of the cardia is strongly associated with an apparently acute oesophago-gastric angle, whereas reflux can usually be produced when this angle is destroyed by herniation of the region of the cardia through the diaphragmatic hiatus or displacement of the stomach to the right either after a too extensive Billroth-I operation or by gas in the splenic flexure of the colon. On the other hand reflux cannot be produced after a careful Heller's operation has destroyed the oesophageal sphincter. If the oesophagus enters the stomach at an angle and the muscularis mucosae heaps up mucosal folds it is difficult to see how these folds can fail to produce a flap valve of the most efficient imaginable form; and to stigmatize this idea as "illogical" is unintelligible.] *Denys Jennings*

1335. **The Gastro-oesophageal Junction in Infancy. A Combined Cineradiographic and Manometric Study**
I. J. CARRÉ and R. ASTLEY. *Thorax* [*Thorax*] **13**, 159–164, June, 1958. 6 figs., 10 refs.

In investigations carried out at the Children's Hospital, Birmingham, on infants under 12 months of age the intragastric and intra-oesophageal pressures were recorded by means of a water-filled polythene tube 2·5 mm. in external diameter connected to a capacitance electromanometer, the tube being slowly withdrawn across the gastro-oesophageal junction. A side opening 1 cm. above the end of the tube was indicated by a radio-opaque marker, and simultaneous cineradiography at 16 frames per second was carried out with an image intensifier, the precise instant of each exposure being recorded on the pressure tracings by means of a second channel. Despite the administration of chloral hydrate to induce a somnolent state it was difficult to obtain records free from extraneous effects due to breath-holding and crying as the tube was withdrawn, and only in 6 cases were the results considered adequate. In 3 of these the stomach and oesophagus were radiologically normal, while the other

3 infants had a " minor degree of partial thoracic stomach ", with reflux but without evidence of stricture formation or spasm, and were being treated for persistent vomiting. A total of 12 withdrawal tracings were obtained from the 3 normal infants; in every case the site at which the descent to intrathoracic pressure began, and in 6 cases the site at which that pressure was reached, was at or below the diaphragmatic level. In 10 of 11 tracings from the 3 with an abnormal gastro-oesophageal junction the site at which the descent to intrathoracic pressure began was at or above the diaphragmatic level, and in all the site at which intrathoracic pressure was reached was above that level. In over half the tracings there was a zone of increased pressure before the fall to general intrathoracic pressure began. These results are interpreted as favouring the hypothesis that an intrinsic closing mechanism exists at the cardia independent of the diaphragm [though the authors seem slightly disturbed by its failure to prevent reflux].

[The shadow of the diaphragm on an *x*-ray film represents that part of the diaphragmatic curve to which the *x*-ray beam was tangential; this is not necessarily the hiatus. The authors' tracings fit in with the impression obtained by radiologists on screening that the presence of a tube in the lower oesophagus is associated with prolongation of the contractions of the vestibule.]

Denys Jennings

1336. **The Importance of Antibiotics in Acute Cholecystitis.** (Значение антибиотиков в лечении больных острым холециститом)
S. Ja. Kisis. *Советская Медицина* [*Sovetsk. Med.*] **22**, 73–77, No. 2, Feb. [received May], 1958. 8 refs.

The author maintains that the use of antibiotics in acute cholecystitis does not have the beneficial effect seen in other infective conditions. Even when given in large doses over a long period these drugs rarely cure the attack and may obscure the clinical picture, while in the event of delay in operation their administration may even be dangerous.

An analysis is presented of 200 cases of acute cholecystitis treated with antibiotics at the Botkin Hospital, Moscow, only those cases being included in which the typical features of gall-bladder inflammation (severe pain, pyrexia, leucocytosis, and evidence of a localized inflammatory process) were present. In 49 cases the patient was discharged without operation after a course of penicillin therapy and general conservative treatment. Of these patients, 27 were followed up over periods of 4 to 10 years; 7 recovered completely, 6 complained of periodic pain, and 14 continued to have attacks as severe as before admission to hospital; 3 of these patients eventually required cholecystectomy.

Of the remaining 151 cases, in 73 the attack, whether recurrent or primary, did not respond at all to antibiotics and operation was carried out at its height; 5 of the patients had actually been receiving penicillin for other conditions when the attack developed. In 68 of these 73 cases penicillin alone was given in doses of 4,000,000 to 8,000,000 units a day depending on the severity of the condition, while in 3 cases streptomycin and in one case sintomycin [a Russian preparation resembling chloramphenicol] was given in addition. In one case a combination of streptomycin and aureomycin was used. At operation complete or partial gangrene of the gall-bladder wall was observed in 19 of these cases, perforation in 39, empyema in 2, and catarrhal changes in 13 (associated with cholangitis in 3 and with sepsis, pancreatitis, and abscess in one case each). In 78 cases operation was performed after conservative treatment had alleviated or completely abolished the symptoms (which, however, had recurred in 11 cases during or after the course of antibiotic therapy). The majority received penicillin for periods varying from 2 to 40 days. At operation signs of acute inflammation were found in 72 cases, gangrene, abscess formation, cholangitis, or perforation of the gall-bladder with peritonitis being present in 29. Only in 6 cases was the condition shown at operation to be cured. There were 13 deaths among the 151 patients treated surgically, and in 9 of these fatal cases antibiotic treatment had not resulted in any improvement. The cause of death was peritonitis in 5 cases (postoperative in 2), " sepsis " in one, " general toxaemia " in 3, hepato-renal failure with septic angiocholitis in 2, and peritonitis following cholecystopancreatitis in 2.

Bacteriological investigations were carried out in 99 of the surgically treated cases, and in 56 *Escherichia coli* was cultured from the gall-bladder. In most of these cases the antibiotic used was penicillin, which is admittedly less effective against intestinal organisms than streptomycin and other agents. However, only in 2 of the 15 cases in which combined antibiotic therapy was given was complete resolution of the inflammatory process observed.

Margot G. Dunlop

1337. **The Clinical Significance of Serum Cyanocobalamin (Vitamin B_{12}) in Liver Disease**
M. Rachmilewitz, Y. Stein, J. Aronovitch, and N. Grossowicz. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **101**, 1118–1125, June, 1958. 8 figs., 17 refs.

This further paper from Hadassah University Hospital, Jerusalem, confirms and amplifies, on a larger number of patients, previous observations reported by the authors (*J. Lab. clin. Med.*, 1956, **48**, 339; *Abstr. Wld Med.*, 1957, **21**, 149). They have found that the serum cyanocobalamin (vitamin-B_{12}) level is greatly increased in active hepatic disease, both in acute viral hepatitis and in chronic cirrhosis during its progressive stages. The highest serum value of vitamin B_{12} (13,000 $\mu\mu$g. per ml.) was observed in a patient with acute necrosis (yellow atrophy) of the liver due to phosphorus poisoning. On the other hand in extrahepatic obstructive jaundice the serum level of vitamin B_{12} was found to remain within the normal range.

The authors thus claim that estimation of the serum vitamin B_{12} level by the method of " modified *Escherichia coli* assay " described by them in 1954 (*Proc. Soc. exp. Biol. (N.Y.)*, **87**, 513), is a valuable method of differentiating between hepatic and extrahepatic jaundice. They also point out that the liberation of stored vitamin B_{12} from the liver (as shown by its excretion in large amounts

in the urine) in viral hepatitis and active cirrhosis results in the loss of a vitamin which plays an important role in erythropoiesis, and may explain the macrocytic anaemia seen in some cases of cirrhosis. It has been shown by other workers that various metals and enzymes may also be released into the circulation in these conditions.

J. W. McNee

1338. **A Clinical and Experimental Study of α-Ketonic Acids in the Blood in Hepatic Disease.** (Les acides alpha-cétoniques sanguins; étude clinique et expérimentale en pathologie hépatique)

P. DE SCHEPPER. *Revue française d'études cliniques et biologiques* [*Rev. franç. Ét. clin. biol.*] **3**, 211–220, March, 1958. 6 figs., 49 refs.

This paper from Medical Clinic B of the University of Louvain describes investigations into the metabolic disturbances associated with hepatic coma which were carried out both on patients with liver failure due to various causes and on rabbits poisoned with carbon tetrachloride. A method for the isolation and quantitative estimation of ketonic acids in biological fluids is described, involving their extraction and conversion into hydrazones, the hydrazones being then separated by paper chromatography. By this method three hitherto unrecognized ketonic acids were detected in human blood, these being derivatives of leucine, *iso*leucine, and valine respectively. In rabbits with liver damage a considerable rise in the α-ketoglutaric acid content of the blood was noted after the administration of glutamic acid, a significant rise in the levels of this acid and of pyruvic acid also occurring without the deliberate infusion of possible precursors.

The problems of hepatic failure and its relation to mental disturbance are fully discussed. The author reaches the conclusion that the principal metabolic disturbance in hepatic coma is a block in intermediary metabolism at the stage of oxidative decarboxylation of pyruvic and α-ketoglutaric acids. *H. Lehmann*

1339. **Circulatory Disorders Affecting the Mesenteric Vessels.** (Нарушения кровообращения в мезентериальных сосудах)

A. P. LEBEDEV. *Клиническая Медицина* [*Klin. Med. (Mosk.)*] **36**, 130–134, No. 6, June, 1958. 8 refs.

With reference to 42 cases observed at the Minsk and the former Pinsk Regional Hospitals the author discusses the causes, clinical aspects, and treatment of circulatory disorders affecting the mesenteric vessels, which are of three types. (1) Embolic blocking of the mesenteric vessels occurs in cases of endocarditis, cardiac valvular disease, and aneurysm of the aorta. (2) Mesenteric thrombosis occurs principally in the elderly and in cases of cardiovascular disease, alcoholism, and syphilis. Exogenous factors such as crush injury may also be responsible. Males are affected much more often than females, and cases in children have been reported only rarely. (3) Until recently embolism and thrombosis have been regarded as the sole causes of blocking of the mesenteric vessels, but it has now been established that an initial stage of spasm of the vessels occurs, leading to endothelial changes and finally to thrombus formation. Clinically, there is an early functional stage characterized by intermittent abdominal pain, constipation, and meteorism, relieved by rest and conservative treatment. As structural vascular changes develop, the pain becomes more constant and severe. Once thrombosis and infarction have occurred necrosis of the intestine and peritonitis will develop if resection is not carried out. Many patients do not survive to this stage.

The author's series consisted of 8 cases of embolism, 14 of arterial thrombosis, 6 of venous thrombosis, 12 of venous with arterial thrombosis, and 2 of functional spasm of the mesenteric vessels associated with hypertension. The superior mesenteric artery was involved in 18 cases, the inferor mesenteric artery in 5 cases, and both in 13 cases. In 11 cases thrombosis occurred postoperatively. At operation the macroscopic appearances were constant—a haemorrhagic infarct affecting a section of intestine and mesentery proportionate in size to the number of vessels involved. The bowel was dark in colour and there was haemorrhagic exudate in the abdominal cavity and in the lumen of the bowel. Symptoms of obstruction were more severe when the upper part of the small intestine was affected.

The diagnosis of intestinal infarction should be easy when there is a known cause of thrombosis and embolism, and the importance of an accurate history is stressed. However, owing to the relative rarity of the condition unfamiliarity with it may lead to misdiagnosis in a high proportion of cases—a figure of 90% is quoted from the literature. The clinical picture of infarction is one of sudden, unbearable abdominal pain, usually diffuse, with collapse, as in internal haemorrhage. There is an ill-defined, mid-abdominal area of dullness on percussion, with muscle guarding. Auscultation reveals absence of peristalsis, and a mass may be felt on deep palpation. Vaginal and rectal examination may help, and the latter may show bleeding. In cases of embolism as opposed to thrombosis the onset of pain is very sudden and localization of the affected area is more definite. But the distinction becomes less clear as thrombosis spreads from the area of embolism. The differential diagnosis is from appendicitis, acute pancreatitis, and extra-uterine pregnancy. Of the author's 42 cases, a correct diagnosis was made in 35; 29 patients died.

In the early functional stage of vascular spasm the patient often comes under the care of the physician, and nitroglycerin may be beneficial. When infarction has occurred, however, surgery must be contemplated. Operation does not remove the cause of thrombosis, and some surgeons refuse to operate if they are certain of the diagnosis. However, resection of the gut was performed on 13 patients, of whom 5 recovered, while laparotomy and peritoneal infiltration with a 0·25% solution of procaine was performed on 6, one of whom recovered. Of the 23 cases treated conservatively, 7 responded. The author advocates the postoperative administration of anticoagulants and vasodilators such as papaverine and atropine. An intravenous infusion of 25% sodium citrate solution with 0·5% of heparin or lumbar block with 0·25% procaine (Vishnevsky's method) may be of value. *Margot G. Dunlop*

Cardiovascular System

1340. **Radio-active Isotope Measurements of Cardiac Output**
R. SHACKMAN. *Clinical Science* [*Clin. Sci.*] **17**, 317–327, May, 1958. 4 figs., 11 refs.

In these studies, carried out at the Postgraduate Medical School of London, human plasma albumin labelled with radioactive iodine was used to determine the cardiac output and plasma volume in 86 unanaesthetized subjects, both ^{131}I and ^{132}I being used in doses of 100 to 150 μc. and 50 to 80 μc. respectively, given intravenously in volumes of 1 to 2 ml. using an accurately calibrated syringe. The radioactivity of the circulating blood was determined by means of a collimated scintillation counter positioned just off the skin one inch (2·5 cm.) to the left of the midline at the level of the second thoracic interspace. In 61 subjects the results thus derived were compared with those obtained by cardiac catheterization and application of the Fick principle. The output of the "ratemeter" coupled to the scintillation counter was connected to a chart recorder and calculations from the activity–time curve thus obtained gave the figures for cardiac output. Plasma volume was also determined in 11 subjects by sampling at 10, 20, and 30 minutes and counting the radioactivity, the results being compared with those by the azovan-blue dilution method.

A highly significant correlation between the values for both cardiac output and plasma volume as determined by the different methods was obtained. The radioactive method offers several advantages: (1) it is safe and causes no discomfort to the patient; (2) it can be repeated several times in rapid succession when ^{132}I is used; (3) the results can be available within one hour; and (4) there is no need for arterial sampling.

[The necessary preparations and calculations, although simple, are too lengthy to be given here, and for details of these the original paper should be consulted.]

I. M. Rollo

1341. **The Influence of Cardiac Catheterization on Cardiac Output.** (Über den Einfluss blutiger Untersuchungsmethoden auf das Herzminutenvolumen)
J. EMMRICH, H. STEIM, H. KLEPZIG, K. MUSSHOFF, H. REINDELL, and B. BAUMGARTEN. *Zeitschrift für Kreislaufforschung* [*Z. Kreisl.-Forsch.*] **47**, 326–337, April, 1958. 1 fig., 26 refs.

During investigation of the cardiovascular system in 33 men and 3 women aged 17 to 50 years at the University Medical Clinic, Freiburg, the cardiac output was determined in 11 of them, of whom 5 were athletes, by the sphygmographic pulse-contour method (after Broemser and Ranke) on the day before the performance of cardiac catheterization and again at least 30 minutes after the catheter had been introduced into the pulmonary artery. A needle was then introduced into the brachial artery and cardiac output was once again determined by sphygmography and the Fick principle. All the tests were performed at least 4 hours after a meal, no premedication being given.

In all but one of the subjects there was a statistically significant increase in cardiac output (by the pulse-contour method) and oxygen consumption after the introduction of the cardiac catheter compared with the corresponding values the previous day. There was no statistically significant difference between the values for cardiac output as determined by the two methods, nor was there a significant difference between the values obtained immediately before and after needle puncture of the brachial artery. The authors conclude that cardiac output measured by the Fick principle, which involves cardiac catheterization, does not give true resting values for this function in man.

A further study showed that the mean heart volume (calculated from a 2-metre chest radiograph taken in the supine position) of 12 athletes was significantly greater than that of a control group of 15 healthy subjects not specially athletic. But there was no statistically significant difference in stroke volume (by the pulse-contour method) between the two groups.

[This study is open to the serious objection that the control determinations by the pulse-contour method were carried out on the previous day. Also, no statement is made as to what, if any, steps were taken to allay the subject's apprehension regarding the catheterization procedure, especially as no premedication was given.]

Gerald R. Graham

1342. **The Role of the Thebesian Veins in Disorders of the Cardiovascular System.** (К вопросу о состоянии тебезиевых сосудов в условиях патологически измененной сердечно-сосудистой системы)
A. I. OZARAJ. *Архив Патологии* [*Arh. Patol.*] **20**, 11–21, No. 5, 1958. 5 figs., bibliography.

The distribution and structure of the Thebesian veins in 35 hearts was studied by the following three methods. (1) The Krainichian–Kretz method of simultaneous irrigation of the cardiac vasculature through both coronary arteries with physiological saline under a constant known pressure, with measurement of the fluid escaping from the coronary sinus and from the Thebesian veins into the heart chambers. (2) Counting the average number of Thebesian veins per sq. cm. in histological sections of the myocardium examined under a constant magnification. (3) The use of an "injection substance" to fill the vascular bed of the heart, the Thebesian veins being revealed by the escape of this substance through their mouths on to the endocardial surface.

The Thebesian veins were found to be sinusoid-like, collapsible vessels with valves whose cusps often contained muscle fibres. The author is of the opinion that these veins subserve a compensatory rather than any nutritive function in the cardiac circulation, for they

reach their highest development not in the hypertrophied, but in the unchanged or less hypertrophied parts of the heart. Apparently " they help the filling of underfilled chambers " of the heart and afford an escape for excess blood from the " overfilled " chamber through their rich anastomoses. Of the 35 hearts studied, only 5 were normal, the other 30 being from 10 patients with valvular heart disease, 10 with cor pulmonale, and 10 with hypertension.

A. Swan

1343. **A Method for the Electrocardiographic Recognition of Atrial Enlargement**

R. MACRUZ, J. K. PERLOFF, and R. B. CASE. *Circulation* [*Circulation*] **17**, 882–889, May, 1958. 4 figs., 12 refs.

The authors describe, from the National Heart Institute, Bethesda, a new method of diagnosing enlargement of the left and right atria which is based on scrutiny of Lead-II tracings in the electrocardiogram (ECG). They use the conventional measurement of P–R interval together with two special measurements, namely, the duration of the P wave and the " P–R segment ", measured from the end of the P wave to the onset of the QRS complex. They consider that the ratio of P duration to P–R segment has diagnostic significance. Thus in the examination of the ECGs of 62 normal adults and 110 patients with congenital or acquired heart disease they found that this ratio is normally between 1·0 and 1·6 for all heart rates and all ages, that a ratio of less than 1·0 indicates right atrial enlargement, and that a ratio of over 1·6 means left atrial enlargement. Further, if the ratio is normal and the P–R interval is increased then a duration of P of less than 0·10 second in children or less than 0·12 second in adults is suggestive of right atrial enlargement. Or again, if the ratio is normal, but both the P–R interval and the duration of P are distinctly prolonged, then combined right and left atrial enlargement can be expected. A theoretical explanation of the prolongation of the different factors is offered.

D. Emslie-Smith

1344. **An Evaluation of the Serum Glutamic Oxalacetic Transaminase Activity in Pericarditis**

R. B. KALMANSOHN and R. W. KALMANSOHN. *American Heart Journal* [*Amer. Heart J.*] **55**, 739–742, May, 1958. 18 refs.

A comparative investigation is reported of the serum glutamic oxalacetic transaminase (G.O.T.) level in 5 cases of non-specific pericarditis and 2 cases of pericarditis complicating myocardial infarction. Increased serum G.O.T. activity was observed in 4 of the 5 patients with non-specific pericarditis, the maximum values being 52, 75, 116, and 165 units. These are comparable with the values expected after minor myocardial necrosis; indeed, in the 2 cases of pericarditis complicating myocardial infarction the serum G.O.T. level rose only to 52 and 56 units respectively.

The authors point out that the finding of increased serum G.O.T. activity in non-specific pericarditis is not in accord with the findings in other reported investigations, in which no deviation from the normal was observed. However, some rise in the serum G.O.T. level has been found in experiments in animals, and is to be expected from the subepicardial myocardial damage which may occur and which probably determines the characteristic changes in the electrocardiogram in pericarditis. It is concluded that the serum G.O.T. level " is only of value in differentiating myocardial infarction from pericarditis if the value is within normal limits ".

Celia Oakley

CONGENITAL HEART DISEASE

1345. **The End-diastolic Filling Pressure of the Right Ventricle in the Presence of Chronically Increased Pressure and Flow Work.** (Der enddiastolische Füllungsdruck bei chronischen Druck- und Volumenbelastungen des rechten Ventrikels)

F. GROSSE-BROCKHOFF and H. H. WOLTER. *Zeitschrift für Kreislaufforschung* [*Z. Kreisl.-Forsch.*] **47**, 481–486, June, 1958. 4 figs., 21 refs.

In 71 patients with isolated stenosis of the pulmonary valve subjected to cardiac catheterization at the Medical Academy, Düsseldorf, the right ventricular end-diastolic pressure and the right atrial peak pressure, as well as the amplitude of the right atrial pressure pulse, all showed a linear correlation with the right ventricular systolic pressure. Thus the higher the ventricular systolic pressure, the higher the atrial peak and ventricular end-diastolic pressures. No such correlation was found in 28 patients with left-to-right shunts of different sizes resulting from atrial septal defect, provided there was no marked pulmonary hypertension.

Gerald R. Graham

1346. **Localization of Left-to-right Cardiac Shunts by Dye-dilution Curves following Injection into the Left Side of the Heart and into the Aorta**

E. BRAUNWALD, H. L. TANENBAUM, and A. G. MORROW. *American Journal of Medicine* [*Amer. J. Med.*] **24**, 203–208, Feb., 1958. 7 figs., 15 refs.

The authors, writing from the National Heart Institute, Bethesda, Maryland, point out the errors which sometimes occur when right heart catheterization techniques are used for detection of left-to-right cardiac shunts, and go on to claim that dye dilution curves obtained from injection of the dye into the left heart enable accurate detection and location of such shunts to be made. They have shown that after injection of dye into the pulmonary veins, left auricle, left ventricle, or aorta and detection of the dye by withdrawal of blood from a peripheral artery through a cuvette densitometer (or by ear-oximeter in children) the resulting dilution curve in normal subjects shows a rapid, sharp ascent and a slower, smooth descent, the primary curve reaching the baseline before recirculation. When a left-to-right shunt is present and the dye has been injected proximal to the origin of the shunt the descent of the primary curve is interrupted by the appearance of dye which has been delayed in going through the pulmonary circulation. When the injection is distal to the origin of the shunt the curve is normal. Thus detection and location of the shunt are possible.

A total of 80 patients were studied by transbronchial left heart catheterization, using azovan blue or indigo carmine as the dye. In 47 of these the presence or absence of a shunt was subsequently determined at operation, in 10 by aortography, and in the remaining 23 by a nitrous oxide test during right heart catheterization. There were no complications of the left heart catheterization and the presence or absence of a shunt was accurately determined in all the patients. Location of the shunt by this means was correct in all patients in whom the exact site of the shunt was known from operation or aortography. The technique was of particular value for distinguishing uncomplicated atrial septal defect (A.S.D.) from interventricular septal defect, A.S.D. from anomalous pulmonary venous drainage and from patent foramen ovale, and patent ductus arteriosus from shunts originating at the root of the aorta. *P. Hugh-Jones*

1347. **The Contour of the Right Atrial Wave in Twenty-seven Cases of Atrial Septal Defect and in Other Cardiac Conditions**

L. M. Haroutunian, C. A. Neill, and A. B. Otis. *Bulletin of the Johns Hopkins Hospital* [*Bull. Johns Hopk. Hosp.*] **102**, 176–194, April, 1958. 15 figs., 23 refs.

After a review of previous studies of the jugular venous pulse the authors of this paper from Johns Hopkins University School of Medicine, Baltimore, report the finding of characteristic changes in the atrial pressure curve in 27 cases of atrial septal defect. After adequate sedation the patients were subjected simultaneously to cardiac catheterization and electrocardiography. The right atrial pressure tracing showed " v " waves at least as great as the " a " waves, so that the whole curve was M-shaped. The " a ":" v " ratio was significantly less than that found in healthy subjects and 15 patients with ventricular septal defect. The pressure tracings in patients with a wide variety of other cardiac conditions, including anomalous pulmonary venous drainage, constrictive pericarditis, and congestive cardiac failure were also studied, but in none was there a pattern similar to that observed in the pressure curve in atrial septal defect.

The authors state that the M-shaped curve may not be seen when atrial septal defect is complicated by severe pulmonary hypertension, gross tachycardia, or arrhythmia. They consider that their findings may be of physiological significance, indicating that the major flow between the atria occurs during atrial filling rather than during systole. *D. Goldman*

1348. **Tricuspid Atresia.** (Atresia tricuspidea)

J. Espino Vela, R. Bernard, B. Portillo, R. Quiroga, and V. Rubio. *Archivos del Instituto de cardiología de México* [*Arch. Inst. Cardiol. Méx.*] **28**, 28–62, Jan.–Feb. [received June], 1958. 23 figs., 30 refs.

In this paper from the National Institute of Cardiology of Mexico an account is given of the findings in 19 cases of tricuspid atresia in patients ranging in age from 2 months to 10 years. Clinically, cyanosis was prominent in most cases, though in one it was subungual only. Clubbing of the fingers was present in 15 cases and squatting was observed in 9. There was a systolic murmur in all cases, being localized to the pulmonary area in 14 and more diffuse in 5; in 9 cases it was accompanied by a thrill and in 2 cases there was also a diastolic murmur in the pulmonary area. Gallop rhythm was present in 13 cases.

Radiographs showed some enlargement of the heart to the left in most cases; however, the small size of the right ventricle in this condition makes it possible for the right auricle to enlarge to the left without affecting the right border of the cardiac silhouette, and only in 9 cases was there a slight filling-out in the region of the right auricle. In the postero-anterior view the cardiac outline may resemble that of the *cœur en sabot* of Fallot's tetralogy, and in the left anterior oblique projection the appearance due to enlargement of the right atrium often simulates that of right ventricular hypertrophy. In 6 such cases the pendular motion of the cardiac mass made accurate diagnosis impossible. Vascularity of the lung fields was usually reduced, though in some cases it was normal or even increased, this last being attributable to back pressure, a patent ductus arteriosus, increase in the bronchial circulation, or origin of the pulmonary artery from the left ventricle. Angiocardiography was performed in 3 cases, in each of which it was demonstrated that blood passed from the right auricle to the left auricle and thence to the left ventricle; in none was it possible to identify the origin of the pulmonary artery.

In 15 of the 19 cases the electrocardiogram showed a biphasic and high P wave in Leads I and II, the first phase being the higher in 13 cases. This finding is indicative of enlarged auricles contracting asynchronously. Left axis deviation was usually present. Cardiac catheterization was carried out in 7 cases, in 4 of which defective oxygen saturation of the pulmonary venous blood—possibly the result of changes in the lungs—was demonstrated. The mean right auricular pressure was within normal limits in 2 cases, markedly increased in 4, and could not be measured in one. Pressure tracings in 4 cases showed a high " a " wave followed immediately by a profound depression. The pressure gradient between the " a " and " x " waves was more than 18 mm. Hg in all cases and more than 25 mm. Hg in one of them. No " c " wave (corresponding to right ventricular systole) was seen. *A. C. F. Green*

1349. **Surgical Treatment for Endocardial Fibroelastosis or Anomalous Left Coronary Artery. Four Years' Experience with Poudrage**

R. N. Paul and S. G. Robbins. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **1**, 694–705, June, 1958. 3 figs., 7 refs.

In a previous paper (*Pediatrics*, 1955, **16**, 147; *Abstr. Wld Med.*, 1956, **19**, 249) the authors described a new method of treatment for endocardial fibroelastosis or anomalous left coronary artery which consisted in poudrage of the pericardium with talc, and described the results in 4 cases so treated. In this further communication from the University of Tennessee, Memphis, they report the results in the 3 survivors from that series and describe 6 further cases of endocardial fibroelastosis treated by this method.

In the whole series of 10 there were 3 operative deaths and one late death. Follow-up of the remaining 6 patients for periods up to 4 years showed that there was a reduction in heart size or in cardiac:thoracic ratio, or both, while in most there was an increase in the rate of growth. While admitting the difficulty of making an absolute diagnosis of endocardial fibroelastosis, the authors consider that in view of the very bad prognosis—a reported mortality of 90% before the age of 2 years—and the inevitable fatal outcome of the untreated condition, these results are sufficiently encouraging to warrant a further trial of the procedure in the treatment of this disorder. *J. R. Belcher*

CHRONIC VALVULAR DISEASE

1350. **The Paradox of Right Ventricular Enlargement in Mitral Insufficiency**
L. Bentivoglio, J. F. Uricchio, and W. Likoff. *American Journal of Medicine* [*Amer. J. Med.*] **24**, 193–202, Feb., 1958. 8 figs., 15 refs.

This report of studies on one male and 3 female patients aged 20 to 40 years in whom surgical exploration (and in 2 cases subsequent necropsy) showed mitral insufficiency without stenosis, is presented by the authors from Hahnemann Medical College and the Bailey Thoracic Clinic, Philadelphia, as being unusual, since all 4 showed electrocardiographic and radiological evidence of right ventricular enlargement which would normally suggest the presence of an additional defect besides mitral incompetence.

Cardiac catheterization studies revealed a reduction in cardiac output in all patients (range 2·1 to 2·8 litres per minute), with an increase in calculated pulmonary vascular resistance. It is the latter condition which, the authors suggest, initiates the right ventricular hypertrophy, and they believe it to arise from a stimulus to the lungs caused by exaggeration of systolic pressures within the left atrium. The necropsy findings in the 2 patients who died showed the pulmonary capillaries to be engorged and the arterioles and veins to have thickening of the intima with narrowing of the lumen.

P. Hugh-Jones

1351. **Emergency Valvotomy after Treatment of Recurrent Crises of Acute Pulmonary Oedema with Hexamethonium.** (Valvulotomie d'urgence au cours de crises subintrantes d'œdème aigu du poumon traitées par l'hexaméthonium)
N. du Bouchet, B. Latscha, and C. d'Allaines. *Anesthésie et analgésie* [*Anesth. et Analg.*] **14**, 1068–1071, Nov.–Dec., 1957 [received May, 1958]. 1 ref.

The authors describe the case of a woman aged 30 who had severe mitral stenosis with episodes of pulmonary oedema. Valvotomy was about to be performed but had to be postponed because of an acute attack during anaesthesia, during which the patient became intensely cyanosed, with abundant frothy sputum and impending circulatory collapse. She was thereupon given 4·6 mg. of hexamethonium. This produced a spectacular improvement, the airways becoming clear, the breathing free, and the circulation improved. Advantage was taken of this state of affairs to perform the valvotomy, which was accomplished without incident. The mode of action of hexamethonium is discussed and the logic of profiting by its beneficial effect to perform an emergency valvotomy is stressed. *Ronald Woolmer*

1352. **The Natural History of Rheumatic Valvular Heart Disease and Its Bearing upon the Results of Surgery for Mitral Stenosis.** [In English]
P. Hall and G. Biörck. *Acta rheumatologica Scandinavica* [*Acta rheum. scand.*] **4**, 70–78, 1958. 3 figs., 5 refs.

Two groups of patients with mitral stenosis—one treated conservatively during 1930–50 and with autopsy confirmation and one operated upon during 1950–55—are compared as regards the long term prognosis. In our opinion it is as yet not possible to draw any definite conclusions about the supposed increased life expectancy after operation for mitral stenosis mostly because the long term prognosis for conservatively treated patients has shown a continuous improvement during the last 10–15 years.—[Authors' summary.]

1353. **Estimation of Severity of Aortic Stenosis by Combined Heart Catheterization**
H. Goldberg, R. C. Smith, and G. Raber. *American Journal of Medicine* [*Amer. J. Med.*] **24**, 853–860, June, 1958. 6 figs., 19 refs.

At Hahnemann Medical College Hospital and the Bailey Thoracic Clinic, Philadelphia, the authors have studied 37 cases of clinically pure aortic stenosis, of which 36 were rheumatic in origin and one congenital. Conventional right heart catheterization was performed, a Cournand needle being placed simultaneously in the brachial artery, and in some cases retrograde catherization of the ascending aorta was carried out. A thin-walled needle was introduced into the left atrium, and through it a polythene catheter was passed into the left ventricle and in some cases into the aorta.

In all cases there was a definite pressure gradient across the aortic valve and in severe stenosis a reduction in the actual blood flow. Estimation of the degree of obstruction at the aortic valve on the basis of these findings suggested that there is a critical valve size, between 20 and 30% of normal (that is, less than one sq. cm.) below which symptoms appear. The reduced cardiac output is thus the resultant of the degree of obstruction, the pressure gradient, and the condition of the myocardium. The left ventricular chamber is often hypertrophied and loses its elasticity and ease of filling. As a result the systolic and diastolic pressures in the left ventricle are raised, giant " a " waves may be seen in the left atrial pressure tracing, and there is an increase in the amount of work performed by the left ventricular myocardium. Pulmonary hypertension, if present, arises from left ventricular failure (which may or may not be obvious), or from increased resistance secondary to pulmonary vascular changes after intermittent rises in pulmonary venous pressure from exercise or failure. It was not

found possible to estimate severity of obstruction from brachial arterial pressure tracings. It is concluded that simultaneous left and right cardiac catheterization is of help in estimating (1) the degree of obstruction and (2) the results of surgical operation on the aortic valve.

J. Warwick Buckler

1354. **Left Ventricular, Central Aortic, and Peripheral Pressure Pulses in Aortic Stenosis**

G. RABER and H. GOLDBERG. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **1**, 572–578, May, 1958. 6 figs., 17 refs.

The authors have performed simultaneous catheterization of the right and left heart in 19 patients with a surgically confirmed diagnosis of pure aortic stenosis and describe the changes in contour found in aortic, brachial, and left ventricular pressure tracings. Although many explanations have been advanced to account for the position of the anacrotic notch, it appears that multiple factors must be considered, and indeed no relationship was demonstrated to stroke volume, pulse pressure, systolic pressure gradient, or calculated aortic valve area. Nor is the presence of the anacrotic notch in the radial pulse pathognomonic of aortic stenosis; it may be found in cases of uncomplicated mitral stenosis, patent ductus arteriosus, coarctation of the aorta, and occasionally with a normal cardiovascular system. The contour of the tracing from the brachial artery was smoother and more peaked than that from the central aorta, and the anacrotic notch occurred later. End-diastolic pressure in the left ventricle was raised in most cases, and the authors believe that, in addition to failure, this is due to alteration in the pressure–volume elasticity relationships related to hypertrophy.

A high incidence of unilateral (systemic) mechanical pulsus alternans was noted in the left ventricular and brachial arterial tracings.

T. Semple

1355. **Isolated Aortic Stenosis—the Late Prognosis.** [In English]

K. H. OLESEN and E. WARBURG. *Acta medica Scandinavica* [*Acta med. scand.*] **160**, 437–446, May 6, 1958. 4 refs.

The results are presented of a long-term follow-up investigation of 42 cases of isolated aortic stenosis seen in private practice and at Rigshospitalet, Copenhagen, between 1933 and 1949. The average age of the patients when first seen was 52·4 years for 31 males and 54·1 years for 11 females. There was a history of rheumatic fever in 14 cases. The diagnostic signs were a loud, rough, aortic systolic murmur, radiological enlargement of the heart, and isoelectric T_1 or left axis deviation. All cases in which there was evidence of aortic incompetence were excluded.

At the time of follow-up (1955–56) all except 3 of the patients had died. The mean survival times were 8·8 years after the first symptom, 4·7 years after the first attack of angina, and 3·2 years after the onset of syncope. The average survival time was shorter in patients with congestive heart failure, marked enlargement of the heart, or arrhythmia. Of 18 cases coming to necropsy aortic stenosis had been diagnosed clinically in 16; in 2 cases the diagnosis had been missed. In all 18 cases moderate or marked isolated aortic stenosis was found post mortem. The classic triad was present in only 3 of these cases.

The authors consider that the results of this investigation provide confirmation of the view that isolated aortic stenosis is a progressive disease which carries a grave prognosis.

David Friedberg

1356. **Tricuspid Stenosis. Clinical Features in Twelve Cases**

T. KILLIP and D. S. LUKAS. *American Journal of Medicine* [*Amer. J. Med.*] **24**, 836–852, June, 1958. 10 figs., bibliography.

Until the advent of the technique of cardiac catheterization the diagnosis of stenosis of the tricuspid valve was often a matter of doubt. In this paper from New York Hospital–Cornell Medical Center, the authors describe the clinical findings in 12 cases of tricuspid stenosis diagnosed by cardiac catheterization and confirmed at operation in 2 cases and at necropsy in 2. Of the 12 patients, 11 were women, and the age range was from 23 to 52 years. In only one case was the tricuspid stenosis the sole lesion, the others having also rheumatic mitral or combined aortic and mitral valvular lesions.

Dyspnoea, including orthopnoea, was one of the most prominent symptoms and showed no sign of improvement after the development of right heart failure or tricuspid insufficiency. Chronic oedema occurred in all 6 patients with atrial fibrillation and in one with normal sinus rhythm. Ascites was present in 6 patients, in 3 of whom it constituted a major problem. Undue fatigue was complained of by 10 patients and was a prominent symptom in 5. The characteristic physical signs of a thrill and a diastolic murmur which was low-pitched, coarse, and seemingly close to the ear were present in 11 cases, the point of maximum intensity being in the 5th left intercostal space parasternally. In all cases the murmur was markedly increased in intensity during inspiration in contrast to a mitral diastolic murmur, which decreases during inspiration. A tricuspid opening snap was heard in only 3 cases.

Radiographic examination showed enlargement of the right atrium in all cases in films taken in the right oblique position, this enlargement being massive in 3 cases with atrial fibrillation associated with other valvular lesions and tricuspid insufficiency. The electrocardiographic findings are described. In 6 patients in normal sinus rhythm and in 2 with atrial fibrillation sharply peaked P waves were present in Lead V1, in 2 cases being taller than the QRS complex; 7 showed ventricular complexes with an "rsr" pattern in right precordial leads. Pulmonary vascular pressures and resistance were lower in patients with co-existing mitral and tricuspid stenosis than in those with a similar degree of mitral stenosis only. Pulmonary symptoms, however, were not entirely absent in these cases and any such advantage was outweighed by the severe fatigue and increasing oedema in patients with a combined stenosis. In no case did the authors observe the so-called ictero-cyanosis

combination described by previous workers, nor do they regard giant " a " waves in the external jugular veins as diagnostic of other than increased right atrial pressure. In the one patient with isolated tricuspid stenosis no giant " a " waves were present. They recommend that when mitral valvotomy is being contemplated co-existing tricuspid stenosis should be sought for and consideration given to exploring the tricuspid valve at operation. Several illustrative case histories are presented, with comments. *J. Warwick Buckler*

DISTURBANCES OF RHYTHM AND CONDUCTION

1357. **Radioiodine Treatment of Paroxysmal Supraventricular Tachycardia in the Euthyroid Patient**
E. CORDAY, H. GOLD, and H. L. JAFFE. *Circulation* [*Circulation*] **17**, 900–906, May, 1958. 5 figs., 8 refs.

This paper from the Department of Medicine, University of California, Los Angeles, reports the results of giving radioactive iodine in oral doses of 6 mc. weekly up to a total of 25 to 30 mc. to 25 euthyroid patients suffering from paroxysms of rapid supraventricular arrhythmia associated with arteriosclerotic or rheumatic heart disease. The result aimed at was relative hypothyroidism rather than clinical myxoedema; if signs of myxoedema appeared thyroid was given.

The result was good in 20 patients, 17 having no further paroxysms and 3 only an occasional paroxysm (induced by surgery or too much thyroid) after treatment. Of the remaining 5 patients, 3 had no tachycardia for 12 to 14 months after treatment, but occasional paroxysms appeared after this; 2 of these patients had angina with the paroxysms before, but not after treatment. In 2 psychotic patients the treatment failed. (An addendum records 8 additional similar cases successfully treated with radioactive iodine.) *D. Emslie-Smith*

1358. **The Dye Dilution Curve in the Evaluation of Mitral Insufficiency**
T. F. HUBBARD. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **51**, 835–841, June, 1958. 4 figs., 6 refs.

Investigations were carried out at the Bishop Clarkson Memorial Hospital (University of Nebraska College of Medicine), Omaha, to evaluate the method of Korner and Shillingford for the estimation of the degree of mitral valvular incompetence. This method is based on the observation that in the presence of valvular incompetence the dye dilution curve, recorded by means of an ear oximeter after the injection of azovan blue into the circulation, shows a wide spread with a decrease in slope, although the appearance time (interval between injection and appearance of the dye at the ear) is relatively normal. The degree of incompetence can, it is claimed, be calculated by comparing the observed slope of the curve with that predicted by calculation from the cardiac output and central blood volume. As a measure of slope the author uses the ratio of disappearance time (determined by extrapolation of the descending limb of the curve to zero dye concentration) to appearance time (D.T.:A.T.).

This adaptation of the method has been applied to 20 normal subjects, 22 patients with mitral stenosis, and 66 patients with varying grades of mitral insufficiency. The degree of mitral insufficiency was assessed clinically, at necropsy, or by the surgeon's finger at operation. The value of the ratio D.T.:A.T. was found to increase steadily from an average of 1·2 in the normal subjects and patients with mitral stenosis to an average of 5·8 in 17 patients judged to have an extreme degree of mitral insufficiency. The correlation between the findings obtained from the dye curve and the clinical or surgical assessment was statistically significant, as was the difference between the mean normal value and the mean value for the group with a minimal degree of insufficiency, although in the latter case there was considerable overlap of individual values and occasional unexpected results were obtained.

The author emphasizes the value of the method, indicating that it has the virtues of simplicity and absence of discomfort or danger for the patient. He considers that the values obtained indicate relative degrees of insufficiency rather than absolute quantitative measurements of the regurgitant flow. *J. McMichael*

CORONARY DISEASE AND MYOCARDIAL INFARCTION

1359. **Further Observations on the Incidence of Coronary Heart Disease in a Rural Area in South-west Scotland**
A. C. KENNEDY and B. COWAN. *Scottish Medical Journal* [*Scot. med. J.*] **3**, 283–287, July, 1958. 12 refs.

In a previous article (Kennedy, *Scot. med. J.*, 1957, **2**, 420) the view was expressed that the current belief that coronary heart disease is " uncommon " in agricultural workers in Great Britain stems from the fact that in 1930–2 the mortality of occupied males in the industry from this cause, after allowing for age differences, was only 32% of that of all occupied males. It was considered, however, that the accuracy of this figure was questionable because at that time the frequency of coronary thrombosis as a cause of death was only just beginning to be recognized and its certification as such would be likely to be less complete amongst agricultural than professional or industrial workers. But even if this were not so the position may have changed since then in view of the fivefold increase in incidence of the disease between 1931 and 1949 and its possible relation to profound changes in the social structure of the country. As evidence that coronary heart disease is no longer uncommon in agricultural workers it was reported that of the male patients admitted to the Dumfries and Galloway Royal Infirmary with coronary heart disease during the 3 years 1954–6, the proportion engaged in agriculture, horticulture, or forestry (24·2%) was very little less than the proportion (26·8%) of the employed male population of the area served by the hospital who were similarly engaged.

In the investigation now reported a different approach was adopted. A private census in Annandale, Dumfriesshire, conducted for another purpose, had shown the population of this area to contain 407 males in the age group 55–64 years. From this group a random sample of 100 were selected, of whom 96 were visited in their homes and later examined at a medical centre, electrocardiograms (ECGs) being taken in every case. Coronary heart disease was diagnosed in 23 cases—in 10 on both clinical and ECG evidence, in 7 on clinical evidence alone, and in 6 on ECG evidence alone. Of these 23 men, 8 (35%) were engaged in agriculture compared with 35 (48%) of those without coronary disease and 43 (45%) of the total sample. The differences are not statistically significant, and the conclusion drawn is that the results of this study also fail to support the view that coronary heart disease is " particularly uncommon " in agricultural workers.

[It would be interesting to know how the authors reconcile these findings with the recently published national occupational mortality data for 1949–53 (*Annual Report of the Registrar-General for Scotland*, 1955). In this Report it is stated that " the higher rates from coronary thrombosis occurred mostly among persons in sedentary occupations ", the highest relative mortality (152 at ages 15 and over, and 133 at ages 15–64, the rate for all males being taken as 100) being found in administrators and directors, while the lowest (76 at ages 15 and over; 56 at ages 15 to 64) occurred amongst agricultural workers.] *E. Lewis-Faning*

1360. **Observations on the Behavior of Various Diagnostic Aids in Myocardial Infarction**
J. R. Durant, G. N. Bowers, and P. H. Twaddle. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **235**, 644–656, June, 1958. 4 figs., 23 refs.

At Hartford Hospital, Connecticut, the diagnostic value in suspected myocardial infarction of the serum levels of glutamic oxaloacetic transaminase (G.O.T.), glutamic pyruvate transaminase (G.P.T.), and lactic acid dehydrogenase (L.D.H.) was compared with that of the serum C-reactive protein content, the leucocyte count, and the erythrocyte sedimentation rate (E.S.R.) (Westergren). Myocardial infarction was diagnosed in 22 of 25 cases on the basis of a raised serum G.O.T. level (which is assumed to occur only in the presence of myocardial necrosis) and the pattern of the electrocardiogram, the diagnosis being definite in 17 cases and probable in 5. The diagnosis was confirmed at necropsy on 6 patients with a definite diagnosis.

The serum G.O.T. level was elevated in all patients with definite and probable infarction and in one patient without infarction. The L.D.H. level was increased in 19 of the 22 patients with infarction, the increase persisting longer than that of the serum G.O.T. level in less than half the patients. An increase in the G.P.T. level was observed in only half the patients with definite infarction, in one of those with probable infarction, and in one without infarction; it was invariably raised when shock complicated infarction. The serum C-reactive protein content increased in 15 cases of definite infarction and all the cases of probable infarction; no false positive results were obtained, but the E.S.R. gave a false positive result in two instances.

The authors conclude that the serum transaminase levels should be determined as a routine in all patients suspected of having myocardial infarction, that the serum G.O.T. and L.D.H. levels are of approximately equal diagnostic value, and that the serum C-reactive protein content is the best non-specific indication of the course of myocardial infarction. *Gerald Sandler*

1361. **" Mild " Myocardial Infarction. Clinical Features and New Method of Management**
M. Prinzmetal, S. M. Weiner, and M. C. Bhuyan. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **1**, 26–37, Jan., 1958. 2 figs., 16 refs.

For many decades the treatment of acute myocardial infarction has routinely included many weeks of rest, regardless of the severity of the attack. Modern technics made it possible to classify most cases of acute myocardial infarction into three categories—" mild ", " moderate ", and " severe ". Some cases are unclassifiable since there is no sharp line of demarcation between these groups. In the typical " mild " case, the patient is young or middle-aged, usually has pain of short duration and looks and feels well 24 to 48 hours after the attack. There is no associated hypertension or previous heart disease. Fever is slight or absent. Leukocytosis is mild and transaminase levels only slightly elevated. Shock, heart failure, gallop rhythm, cardiac enlargement and other serious phenomena do not occur in these cases.

In our series of 200 cases of acute myocardial infarction, the " mild " cases constituted 15% of the total number but it is believed that this is a falsely low figure. A review of 400 cases of fatal acute myocardial infarction observed over a 6½-year period, failed to reveal any patient with a " mild " case who died during or soon after the attack. The immediate mortality rate in " mild " cases must be extremely low. Certainly, it is much less than the average in all myocardial infarctions.

It is absolutely necessary to take into account the complete clinical picture, including all available laboratory data, in order to diagnose and properly classify cases of acute myocardial infarction. Although the electrocardiogram is usually of great assistance in the diagnosis of myocardial infarction, the physician should be familiar with its limitations.

A method of management of " mild " cases is described in which gradually increasing activity is permitted after 2 weeks of rest and observation. Twenty-two cases have been successfully treated in this manner. Seven cases successfully treated with less than the usual long-term period of rest have been followed for over a year. No untoward effects were observed in any of these patients. Definite psychologic and financial benefits were apparent in all. One of these patients remained ambulatory after his first infarction but survived 29 years.

Clinical evidence is presented which indicates that the danger of cardiac rupture or aneurysm formation in cases of mild myocardial infarction is minimal. This conclusion is supported by the finding that it is virtually

impossible to rupture small infarcted areas in dogs 2 weeks after coronary ligation.

In view of the very low mortality and paucity of complications in " mild " cases, it seems neither necessary nor desirable to subject such patients to the same rigorous and prolonged treatment required for more severe cases. Furthermore early activation of these patients results in distinct physical, psychologic and financial benefits.—[Authors' summary.]

1362. **Anticoagulant Therapy in Acute Myocardial Infarction**

R. L. RICHARDS. *Scottish Medical Journal* [*Scot. med. J.*] **3**, 235–244, June, 1958. 36 refs.

The treatment of myocardial infarction is discussed with reference to the results obtained in 267 patients admitted to the Western Infirmary, Glasgow, between 1949 and 1956, 176 of whom received anticoagulants. Approximately one-third of the patients died in hospital from the effects of infarction. Mortality was higher in females (40·3%) than in males (30·5%), but the difference was less than that reported by others. The majority of the patients were admitted within 24 hours of the onset of symptoms. The cases were classified according to the criteria of Russek and Zohman as " good-risk " or " bad-risk " cases. In the good-risk group 4 out of 109 patients (3·7%) died and in the bad-risk group 84 out of 145 (58%) died. Of the 267 patients, 30 died within 24 hours of admission; of the 176 who received anticoagulant treatment, 35 (20%) died, and of 61 who did not receive anticoagulants, 24 (39%) died.

During the 5-year period 1944–8 113 patients were admitted to the hospital with myocardial infarction and 34 (30%) died. Thus over a 13-year period the death rate remained remarkably constant and the introduction of anticoagulants in 1949 appeared to have little influence. The author does not consider that the high death rate in the present series was due to thrombo-embolic complications (only 6 deaths from this cause) or to poor control of anticoagulant therapy. He concludes that the results of the investigation have not provided " convincing proof of the beneficial effects of anticoagulant therapy in acute myocardial infarction ".

A. I. Suchett-Kaye

HEART FAILURE

1363. **Studies on the Hydrogen Ion Concentration, Oxygen Saturation, and Carbon Dioxide Tension of the Arterial Blood in Patients with Cardiac Dyspnoea.** [In English]

E. MOLTKE and H. WORNING. *Acta medica Scandinavica* [*Acta med. scand.*] **160**, 397–404, April 15, 1958. 2 figs., 28 refs.

In order to determine the difference between the mechanisms responsible for cardiac and for pulmonary dyspnoea the authors, at Blegdams Hospitalet, Copenhagen, estimated the *p*H, the carbon dioxide tension (pCO_2), and the oxygen saturation of arterial blood in 55 patients with chronic cardiac decompensation and 55 patients with dyspnoea due to chronic lung disease. The patients with cardiac dyspnoea showed normal or slightly reduced oxygen saturation, normal or reduced pCO_2, and a normal or raised *p*H, while the patients with pulmonary dyspnoea had low oxygen saturation, elevated pCO_2, and decreased *p*H. In patients with cardiac decompensation arterial oxygen saturation was lowest in the presence of basal congestion and hydrothorax. No difference was observed between the blood gas values in patients with mild cardiac dyspnoea and those in patients with severe cardiac dyspnoea.

The authors conclude that dyspnoea in chronic cardiac decompensation is not causally related to the level of oxygen saturation or to the pCO_2 of arterial blood, but that the changes in blood gas values are due to increased demands on ventilation together with local diffusion problems.

Bernard Isaacs

1364. **Diuretic Action of Two Carbonic Anhydrase Inhibitors in Congestive Failure**

H. GOLD, T. H. GREINER, L. WARSHAW, N. T. KWIT, and A. GANZ. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **167**, 814–818, June 14, 1958. 2 figs., 19 refs.

At Beth Israel Hospital and the Hospital for Joint Diseases (Cornell University Medical College), New York, a study was made of the diuretic action of the carbonic anhydrase inhibitors acetazolamide and ethoxzolamide (6-ethoxy-2-benzothiazolesulphonamide; "cardrase"). The method employed was to measure the loss of body weight of ambulant patients with congestive heart failure during the first 24 hours after the oral administration of the drugs in various doses, the results being compared with those observed in the same patients after the intramuscular injection of standard doses of meralluride.

Acetazolamide was given on 417 occasions in doses varying between 125 and 1,000 mg. [The number of patients is not specified, but was " 25 or more ".] The resulting weight loss was not proportional to the dose, and at all levels of dosage approximated to that following the injection of 0·5 ml. of meralluride. When acetazolamide and meralluride were given together to 39 patients in various doses the acetazolamide did not enhance the diuretic response to meralluride.

Ethoxzolamide was given on 178 occasions in doses varying between 62·5 and 250 mg. to 42 patients. A satisfactory dose–response curve was obtained, the 250-mg. dose giving a diuretic response corresponding to that observed after the injection of 0·7 ml. of meralluride. Ethoxzolamide gave rise to diarrhoea, colic, and vomiting, the incidence and severity of which increased with the dose. Symptoms severe enough to prevent the continuation of treatment except under protest occurred in one-fifth of the patients receiving the largest dose.

Charles Rolland

1365. **Renal Adaptations to Postural Changes in Chronic Congestive Heart Failure**

R. A. NORDYKE and M. L. PEARCE. *American Heart Journal* [*Amer. Heart J.*] **56**, 202–211, Aug., 1958. 3 figs., 22 refs.

Clinical Haematology

1366 (a). **Haematological Aspects of Old Age. I. Preliminary Considerations.** (L'aspect hématologique de la vieillesse. I. Considérations préliminaires)
N. GINGOLD. *Sang; biologie et pathologie* [*Sang.*] **29**, 230–237, 1958. Bibliography.

1366 (b). **Haematological Aspects of Old Age. II. The Peripheral Blood.** (L'aspect hématologique de la vieillesse. II. Le sang périphérique)
N. GINGOLD, A. PODHORSCHI, C. CUTCUDACHE, F. ENACHE-CIUNTU, and A. BALAN. *Sang; biologie et pathologie* [*Sang*] **29**, 237–242, 1958.

1366 (c). **Haematological Aspects of Old Age. III. The Bone Marrow.** (L'aspect hématologique de la vieillesse. III. La moelle osseuse)
N. GINGOLD, C. CUTCUDACHE, I. GORESCO, and A, PODHORSCHI. *Sang; biologie et pathologie* [*Sang*] **29**, 243–246, 1958. 2 refs.

The first of these three papers from the Institutes of Geriatrics and of Haematology and Blood Transfusion, Bucharest, presents a rapid review of over 80 publications dealing with haematological values in old age, from which it emerges that the most unequivocal signs of haematological change with advancing age are the slight reductions in haemoglobin level, erythrocyte count, and haematocrit value. These changes are more marked in men than in women, thus reducing the sex differences found between these values in younger subjects. No other important change in the peripheral blood has been described, while reports of the changes in the bone marrow have been contradictory. In one such study carried out on bone marrow from 150 subjects over the age of 60 the findings included an increase in connective tissue and an absence of hyperplasia, even in the presence of anaemia.

In the second and third papers the authors present their own findings in the peripheral blood and the bone marrow respectively of 80 subjects between the ages of 60 and 106 whose state of health was regarded as physiologically normal. The principal finding was a reduction in haemoglobin values in both men and women, being more marked in men and often accompanied by hypochromia of the erythrocytes. Plotting of Price-Jones curves in 36 cases showed that in old age there was a tendency to macrocytosis and leptocytosis. Total leucocyte counts were often below the limits of normal for younger subjects, and both lymphopenia and eosinopenia were noted. Unusual cells, such as Türck cells and plasma cells, were found more frequently than normal in the peripheral blood. The serum iron levels were lower than normal, and in respect of this finding as well as of the erythrocyte count and haemoglobin and haematocrit values the authors confirm that the normal sex differences are less marked in older people.

In the study of the bone marrow satisfactory samples were obtained from 66 subjects, and these were examined in several ways. A marked reduction in marrow cellularity was found in 87% of cases, this being in part due to a notable reduction in erythropoiesis, in some cases associated with appearances suggestive of an arrest of maturation. Apparent maturation arrest affecting the granulocyte series was also observed, but less frequently. In contrast to the frequent lymphopenia in the peripheral blood, an increased number of lymphocytes were often to be seen in the bone marrow. Other marrow cells apparently increased in number in old age included reticulum cells and mast cells. A study of histological sections confirmed the finding of reduced numbers of marrow cells, 13 out of 18 sections being regarded as hypocellular. The frequency of polyploidy in the bone marrow of old people is also remarked upon.

A. G. Baikie

HAEMORRHAGIC DISEASES

1367. **Hereditary Capillary Purpura (Von Willebrand's Disease)**
A. R. HORLER and L. J. WITTS. *Quarterly Journal of Medicine* [*Quart J. Med.*] **27**, 173–185, April, 1958. 1 fig., bibliography.

The authors classify hereditary purpura as follows: (1) hereditary capillary purpura (von Willebrand's disease), in which the defect is apparently confined to the walls of the capillaries; (2) hereditary thrombocytopathic purpura (Glanzmann's disease), in which there is a platelet defect associated with poor clot retraction, reduced prothrombin consumption, and impaired thromboplastin generation; (3) hereditary thrombocytopenic purpura, in which the platelet defect is quantitative; and (4) hereditary purpura, in which a capillary defect is combined with a clotting-factor deficiency. The clinical picture and diagnosis of the first of these, which is the most common, are discussed with reference to 20 cases seen at the Radcliffe Infirmary, Oxford. Evidence is presented that the pattern of inheritance is inconstant, that the sexes are affected almost equally, and that the disease is usually recognized early in life, sometimes at birth. Haemorrhage may be spontaneous or provoked by trauma, and there is often evidence of a cyclical tendency to bleeding. Traumatic haemorrhage is important and frequently troublesome, but postoperative haemorrhage is variable and unpredictable. In the authors' series the bleeding time was over 6 minutes in all except 2 cases, and the response to the tourniquet test was positive in 7 out of 18 cases. The authors state that the latter varied from time to time in the same patient. The abnormal appearance of the nail-bed capillaries which has been observed by a number of other workers was seen in 5 out of 7 cases.

The features of the other types of hereditary purpura are briefly outlined.

A. Brown

1368. **Antihemophilic Globulin Assay following Plasma Infusions in Hemophilia**
A. S. DOUGLAS. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **51**, 850–859, June, 1958.

The object of this investigation was to determine the efficacy of transfusions of fresh-frozen plasma in raising the level of anti-haemophilic globulin (A.H.G.) in the blood of haemophilic patients. Plasma was taken from blood collected for transfusion, cooled rapidly, and then stored at −20° C. The author states that this form of plasma is much cheaper to prepare than lyophilized dried A.H.G. and that no troubles were experienced from the volume of plasma that had to be used. For assay of the level of A.H.G. a technique based on the thromboplastin generation test was employed and some other tests were also carried out for checking. The investigation confirmed the difficulties others have encountered in raising the level of A.H.G. In order to raise it to 14% one litre of plasma had to be rapidly infused, and to maintain this level one litre had to be given every 6 to 12 hours. An A.H.G. level of 14% had some haemostatic effect, but higher levels were better, especially if surgery was contemplated. An A.H.G. level of less than 1% was maintained for 24 hours after plasma infusion, but its subsequent fate is not clear. Nevertheless, experience suggests that plasma transfusions are adequate to control bleeding after tooth extraction or haematuria in haemophilic patients, and therefore fresh-frozen plasma, which remains suitable for use for several weeks, should be available.

M. C. G. Israëls

ANAEMIA

1369. **Role of the Spleen and Effect of Splenectomy in Sickle Cell Disease**
C. C. SPRAGUE and J. C. S. PATERSON. *Blood* [*Blood*] **13**, 569–581, June, 1958. 31 refs.

It has long been known that erythrocytes from patients with sickle-cell anaemia have a shortened survival time on transfusion into normal individuals, but that the life span of cells from carriers of the sickle-cell trait is not so reduced. The present article, reports investigations into the relation between the survival time of erythrocytes from patients with sickle-cell anaemia and sickle-cell–haemoglobin-C disease and the size of the patient's spleen. The life span of the erythrocytes was measured by labelling a sample of cells with radioactive chromium (^{51}Cr) and observing the persistence of the isotope in the blood stream after their reinjection (or injection into a normal subject).

There was a great difference between the survival of cells from 7 patients with sickle-cell anaemia and splenomegaly, the average half-life of which was 3·7 days, and that of cells from 7 patients with sickle-cell anaemia but no splenomegaly, the average half-life of which was 10 days. After splenectomy had been performed on 5 patients in the former group the half-life of their erythrocytes rose to an average of 11·4 days. The phenomenon of autosplenectomy is well known in sickle-cell anaemia, recurrent infarction gradually reducing the amount of surviving splenic tissue until nothing but a small fibrotic organ remains. It is therefore interesting to note that the average half-life of erythrocytes from the patients with sickle-cell anaemia but no splenomegaly, which was 10 days on reinjection into their own blood, was only 4·7 days on transfusion into normal recipients. The implications of these findings in respect of the treatment of sickle-cell anaemia are discussed. There seems to be no doubt that splenectomy can be beneficial in children with sickle-cell anaemia in whom erythrocyte survival is reduced to a half-life of less than 6 days.

The average half-life of erythrocytes from 7 patients with sickle-cell–haemoglobin-C disease, 3 of whom had splenomegaly, was 15·7 days. Splenectomy was performed on 2 patients, after which the half-life remained unchanged in one and increased from 15 to 21 days in the other. In 2 out of 3 cases the half-life of the cells was reduced on transfusion into normal recipients, but the authors consider their data to be insufficient to allow conclusions to be drawn. *H. Lehmann*

1370. **Sickle Cell Disease in India**
R. N. SHUKLA, B. R. SOLANKI, and A. S. PARANDE *Blood* [*Blood*] **13**, 552–558, June, 1958. 3 figs., 21 refs.

From the Medical College, Nagpur, India, the authors report the existence of a focus of sickle-cell disease in that region. Detailed investigations were carried out on 5 local residents who belonged either to the Mahar or to the Kosthi community. In 4 cases only haemoglobin S was found in the blood on electrophoresis, and family studies, so far as it was possible to pursue them, supported the diagnosis of homozygous sickle-cell anaemia. In the blood of the fifth patient, whose father was homozygous for haemoglobin A and whose mother was a carrier of the sickle-cell trait, both haemoglobin S and haemoglobin A were present, the proportion of the former being the greater. Here the diagnosis of sickle-cell–thalassaemia was made. *H. Lehmann*

1371. **Complementary Notes on Drepanocytosis. I. Sicklaemia and Malaria. II. Sicklaemia and Hookworm Anaemia.** (Notes complémentaires sur la drépanocytose. I. Sicklémie et malaria. II. Sicklémie et anémie par ankylostomiase)
J. LAMBOTTE-LEGRAND and C. LAMBOTTE-LEGRAND. *Annales de la Société belge de médecine tropicale* [*Ann. Soc. belge Méd. trop.*] **38**, 45–53, and 55–56, Feb. 28, 1958. 40 refs.

In this retrospective review of the records of children under the age of 5 seen at the Red Cross Paediatric Clinic, Léopoldville, Belgian Congo, during the period 1949–56, the authors have compared the incidence of the various forms of malaria and of ankylostomiasis as between children with and those without the sickle-cell trait (heterozygotes). Of 265 cases of uncomplicated malaria, only 21% occurred in sicklaemic children, while all but 2 of the 77 cases of malignant malaria, and all 23 deaths due to malaria, occurred in non-sicklaemic children. The incidence of the sickle-cell trait in children with ankylostomiasis was 23% of 205 cases, that is, roughly the same as the incidence of the trait in the general child

population in that area. It is concluded that sickling (drepanocytosis) offers some degree of protection against malignant malaria, but not against benign malaria or severe hookworm disease. *David Friedberg*

1372. **Hereditary Persistence of Foetal Haemoglobin Production, and Its Interaction with the Sickle-cell Trait**
G. F. JACOB and A. B. RAPER. *British Journal of Haematology* [*Brit. J. Haemat.*] **4**, 138–149, April, 1958. 2 figs., 26 refs.

In the last few years it has become recognized that the results of the simultaneous inheritance of the traits for thalassaemia and sickling are much more variable than was at first supposed. Some individuals heterozygous for both genes show no abnormality other than sickling and the presence of target cells; in some cases with more than 70% of haemoglobin S the anaemia is only slight, while in others only haemoglobin S, with a small amount of haemoglobin F, can be found.

The present paper from the Medical Laboratory, Kampala, Uganda, deals with yet another variation in which a thalassaemia-like genetic factor is present which is responsible for suppression of haemoglobin-A production and persistence of foetal haemoglobin in the carrier of the sickle-cell trait, and for persistence of foetal haemoglobin in the haemoglobin-A homozygote. The cases are described of 4 Africans who were not anaemic, but whose haemoglobin resembled in constitution that of sickle-cell anaemia. In 2 instances the patient's family could be examined; it was ascertained that there was no thalassaemia and also that the propositi could not possibly be homozygous for the sickle-cell gene. In each case haemoglobin F was found in the blood of one parent.

The authors review the previous literature and conclude that persistence of foetal haemoglobin into adult life exists as a genetic entity, unassociated with other haematological abnormalities. *H. Lehmann*

1373. **Studies in Thalassaemia**
I. S. BAILEY and T. A. J. PRANKERD. *British Journal of Haematology* [*Brit. J. Haemat.*] **4**, 150–155, April, 1958. 5 figs., 7 refs.

Though thalassaemia major is generally regarded as a haemolytic anaemia, erythrocytes from patients with the disease having an abnormally short survival time on transfusion into normal subjects, studies of the rate of production of haemoglobin and erythrocytes suggest that the principal defect in thalassaemia is a deficiency in the fabrication of erythrocytes, and that the severity of the anaemia is largely determined by failure of the bone marrow to respond to the stress of haemolysis. At University College Hospital, London, the authors have used radioactive iron (^{59}Fe) and chromium (^{51}Cr) to measure erythrocyte survival and marrow activity and to determine the sites of erythrocyte destruction and production in 2 adult Cypriots suffering from thalassaemia. The rate of reappearance of ^{59}Fe in the blood after its injection 24 hours previously was regarded as an index of the rate of formation of haemoglobin, and the rate of disappearance of ^{51}Cr after the injection of erythrocytes labelled with the isotope as a measure of the rate of their destruction.

It was demonstrated in both patients that the destruction of the erythrocytes was accelerated and that there were two groups of cells, one with a mean life of a few days (which were largely destroyed in the spleen) and the other with a mean life of about 30 days. Erythrocyte production per unit of bone marrow was reduced, but there was an expansion of the volume of blood-forming marrow tissue, so that in fact total erythrocyte production was greater than normal. It would appear, therefore, that whether or not a thalassaemic patient becomes anaemic will depend on the degree to which this increase in the production of erythrocytes can offset their loss by haemolysis. *H. Lehmann*

1374. **Iron Enzymes in Iron Deficiency. II. Catalase in Human Erythrocytes**
E. BEUTLER and R. K. BLAISDELL. *Journal of Clinical Investigation* [*J. clin. Invest.*] **37**, 833–835, June, 1958. 3 figs., 13 refs.

Experiments have shown (Beutler, *Amer. J. med. Sci.*, 1957, **234**, 517; *Abstr. Wld Med.*, 1958, **24**, 33) that, contrary to previously held views, the cytochrome-C content of the liver and kidneys is diminished in iron-deficiency anaemia. These experiments were carried out on rats, and it has not been possible to repeat them on human beings because of the difficulty of obtaining large specimens of cytochrome-containing tissue. However, another iron enzyme, catalase, is readily available in erythrocytes, and at the University of Chicago Clinics catalase activity in erythrocytes was studied in 11 patients with iron-deficiency anaemia and 9 healthy subjects.

In the patients with iron-deficiency anaemia there was no change in the catalase activity per ml. of erythrocytes. Other findings were a slight decrease in catalase activity per 10^{10} erythrocytes and a well-marked increase in catalase activity per gramme of haemoglobin. These findings, however, reflected the microcytosis and low erythrocyte haemoglobin concentration in iron-deficiency anaemia. It would appear, therefore, that the mechanism synthesizing catalase is more successful in competing for available iron than is the mechanism synthesizing haemoglobin. *R. F. Jennison*

1375. **Folic-acid Studies in Megaloblastic Anaemia Due to Primidone**
I. CHANARIN, P. C. ELMES, and D. L. MOLLIN. *British Medical Journal* [*Brit. med. J.*] **2**, 80–82, July 12, 1958. 3 figs., 12 refs.

The utilization of folic acid in megaloblastic anaemia due to the anticonvulsant drug primidone was studied at Hammersmith Hospital, London, in a female patient aged 44 years. Administration of 3 mg. of folic acid by mouth was followed by a peak serum folic acid level of 73 μmg. per ml., indicating normal absorption of this substance. The clearance of folic acid from the plasma after an intravenous injection of 15 μg. per kg. body weight was normal when determined: (1) before treatment, while the patient was still taking primidone; (2) when primidone had been withdrawn and a large dose

of ascorbic acid had been given; and (3) after administration of large doses of folic acid. This normal rate of clearance was in contrast to the abnormally rapid clearance observed in patients with a megaloblastic anaemia due to folic acid deficiency. The anaemia in the authors' case responded to treatment with folic acid.

It is concluded that megaloblastic anaemia in patients receiving anticonvulsant drugs is not due to folic acid deficiency, but to interference by the drug with the utilization of folic acid. *J. L. Markson*

1376. **Intrinsic-factor-inhibiting Substance in Serum of Orally Treated Patients with Pernicious Anaemia**
M. SCHWARTZ. *Lancet* [*Lancet*] **2**, 61–62, July 12, 1958. 12 refs.

It is now well known that a considerable proportion of patients with pernicious anaemia show an incomplete response to prolonged oral treatment with purified hog pyloric mucosa plus vitamin B_{12} owing to some block in the intestinal absorption of the vitamin; it has been shown that this block does not occur when the vitamin is given with homologous intrinsic factor. As part of an investigation into this problem the author, working at Bispebjerg Hospital, Copenhagen, has examined the possibility that an antibody against intrinsic factor might be responsible for the block. He made use of the urinary excretion test of Schilling, 0·5 μg. of vitamin B_{12} labelled with 0·1 μc. of radioactive cobalt (^{60}Co) being given orally followed 2 hours later by 1 mg. of unlabelled vitamin, the 24-hour urinary excretion of the labelled vitamin being then estimated. The test for antibody against intrinsic factor was carried out by mixing 100 mg. of hog pyloric mucosa with a small quantity of water and then with 50 ml. of serum at room temperature. After 10 minutes this mixture was given with the test dose of radioactive vitamin.

By these tests it was shown that serum from healthy persons and from 6 patients with untreated pernicious anaemia did not contain any substance inhibiting intrinsic factor. But in the sera of 16 out of 21 patients with pernicious anaemia treated orally for more than a year with preparations of vitamin B_{12} plus hog gastric mucosa there was significant anti-intrinsic-factor activity. Investigation of 13 of these 16 patients whose sera showed such activity revealed evidence in all of a blockage of intestinal absorption of vitamin B_{12}. Of the 5 patients in whom no antibodies were demonstrated, 3 were investigated and evidence of blocked absorption of the vitamin was found in 2. The serum of 3 out of 6 patients with pernicious anaemia who had received crude stomach preparations by mouth for long periods showed gross anti-intrinsic-factor activity, yet in 5 of these cases no abnormality of intestinal absorption was found, and only slight malabsorption in the sixth; while in 2 patients with pernicious anaemia treated by injections of vitamin B_{12} no intrinsic-factor inhibition was found. Lastly, in 2 out of 3 sera which were known to inhibit hog mucosa activity there was pronounced inhibition also of intrinsic factor from the mucosa of the human gastric fundus.

The author concludes that intrinsic-factor-inhibiting activity in the serum of patients with pernicious anaemia treated for long periods with oral preparations is not the sole cause of the blockage of intestinal absorption of vitamin B_{12}. *D. G. Adamson*

1377. **Oral Treatment of Pernicious Anaemia with Vitamin B_{12} and Purified Intrinsic Factor. II. Studies on the Reduced Effect of Prolonged Treatment.** [In English]
A. KILLANDER. *Acta Societatis medicorum Upsaliensis* [*Acta Soc. Med. upsalien.*] **63**, 1–13, 1958. 4 figs., 24 refs.

A previous study of the results in pernicious anaemia of oral administration of "bifacon", a preparation of vitamin B_{12} (cyanocobalamin) combined with purified hog intrinsic factor, showed that of 24 patients so treated, 10 had haematological or neurological relapse and 9 had abnormally low serum vitamin-B_{12} levels, and further that the anaemia in these refractory cases responded to administration of another, similar, preparation. The author therefore studied absorption of the vitamin, using the Schilling radioactive vitamin B_{12} absorption test in 6 of the patients with low serum levels of the vitamin and in 6 of those in relapse. The reduced effect of bifacton was found to be due to blocked absorption of the vitamin, but the reason for this is not known. The resistance does not appear to depend on the heterologous origin of the intrinsic factor. *R. B. Thompson*

1378. **The Effects of ACTH and Cortisone in Experimental Haemolytic Anaemias in Guinea-pigs. Studies on Anaemias Due to Heterologous Anti-red-cell-serum and on the Anaemia of Chronic Lead Poisoning**
A. G. BAIKIE and R. PIRRIE. *Scottish Medical Journal* [*Scot. med. J.*] **3**, 264–273, June, 1958. 5 figs., 30 refs.

In this paper from the Royal Infirmary, Glasgow, carefully controlled studies are reported of the effects of corticotrophin (ACTH) and of cortisone on two types of experimentally produced haemolytic anaemia in guinea-pigs. Several explanations of the beneficial effects of steroid hormones in acquired haemolytic anaemia in man have been suggested—namely, reduction in antibody formation, interference between the union of erythrocytes and antibody, depression of macrophage activity, and stimulation of erythropoiesis. In the present series of experiments on guinea-pigs given various doses of an anti-guinea-pig-erythrocyte serum or lead nitrate, administration of steroid hormones was without benefit. A small rise in the reticulocyte count was observed in the experimental animals after ACTH, but this was not associated with any change in the haemoglobin level or in the excretion of urobilinogen. A rise in the reticulocyte count was also noted when the animals were given only the propylene-glycol vehicle of the ACTH, and it was concluded that the rise was due to premature delivery of reticulocytes from the bone marrow, or to delayed ripening, or to both. The rise was not observed in animals receiving lead after splenectomy.

The authors discuss the failure of steroid hormones to influence the course of experimental haemolytic anaemia and the frequent success of these hormones in man when the reaction to the direct Coombs test is positive. They conclude that the two types of anaemia differ in some fundamental respect. *J. V. Dacie*

Respiratory System

1379. **Giant-cell Granuloma of the Respiratory Tract (Wegener's Granulomatosis)**
E. W. WALTON. *British Medical Journal* [*Brit. med. J.*] **2** 265–270, Aug. 2, 1958. 4 figs., bibliography.

The pathogenesis, clinical features, and treatment of Wegener's granulomatosis are discussed with reference to 10 cases seen by the author and 46 collected from the literature. Wegener's granulomatosis is a rare disease characterized by ulcerative lesions in the upper and lower respiratory tracts with, in the later stages, involvement of other organs, particularly the kidneys. The granulomatous changes are frequently accompanied by polyarteritis nodosa. In spite of the varied symptomatology and pathological changes it is likely that this disease process is a separate and distinct entity. There is a considerable amount of evidence that hypersensitivity plays some part in the aetiology.

The prognosis is very poor, most patients dying within 6 months, generally from renal or respiratory failure. However, survival up to 4 years is not unknown. Malignant granuloma and polyarteritis nodosa may simulate Wegener's syndrome very closely. Biopsy material, however, can often be obtained and the radiological appearances in the lungs—large rounded or oval opacities, sometimes cavitated—are fairly typical. Treatment consists in irradiation of the local lesions, control of secondary infection with suitable antibiotics, and administration of steroids once the ulceration has healed.

[This paper deserves study as some useful statistical details are given. The syndrome is probable frequently misdiagnosed or overlooked.] *Paul B. Woolley*

1380. **Importance of *Staphylococcus aureus* in Pneumonia in the 1957 Epidemic of Influenza A**
L. ROBERTSON, J. P. CALEY, and J. MOORE. *Lancet* [*Lancet*] **2**, 233–236, Aug. 2, 1958. 3 figs., 3 refs.

During September and October, 1957, when influenza due to the Asian variety of influenza-A virus was epidemic, 140 patients with pneumonia were admitted to the City General Hospital, Sheffield. *Staphylococcus aureus* was cultured from specimens of the sputum or from necropsy material in 38 cases, pneumococci in 12 cases, and *Haemophilus influenzae* in 5. There were 18 deaths in the group with staphylococcal infection compared with 16 among the remaining 102 patients. Strains of *Staph. aureus* resistant to penicillin, aureomycin (chlortetracycline), streptomycin, and the sulphonamides were found in 13 patients who were probably infected in hospital. Among patients with chronic chest disease as well as those who were previously healthy the mortality was much higher when *Staph. aureus* was present. The authors state that the results of virus studies, coupled with an increase in notifications of cases of pneumonia and in the hospital admission rate, tended to support the view that the condition in most cases was post-influenza-A pneumonia. *I. Ansell*

1381. **Lung Abscess and Pneumonia Complicating Influenza**
J. M. ANGELONI and G. W. SCOTT. *Lancet* [*Lancet*] **1**, 1254–1256, June 14, 1958. 3 figs., 7 refs.

During October, 1957, 41 patients with pneumonic complications of influenza were admitted to hospitals of the Bromley (Kent) group, which serve a population of about 250,000 among whom influenza was then epidemic. Of 13 patients with pre-existing chronic chest disease, 6 died; of the remaining 28, who were previously fit, 3 died of fulminating influenzal pneumonia and 8 developed lung abscess. *Staphylococcus aureus* was isolated on culture of the sputum of one of the patients with pre-existing chest disease and of 14 of those who were previously fit; in 6 of the latter group the organism was insensitive to penicillin. Sputum culture was positive for *Staph. aureus* in 6 of the cases of lung abscess, the organism being resistant to penicillin in 3.

B. Golberg

1382. **Bronchogenic Carcinoma in Young Persons**
W. J. HANBURY. *British Journal of Cancer* [*Brit. J. Cancer*] **12**, 202–206, June, 1958. 8 figs., 6 refs.

A brief review of the literature revealed reports of 60 cases of bronchial carcinoma in patients under the age of 21 years, but adequate information on the histological findings was available in only 24 of these. The present author describes 2 further cases in children and a third in a young man of 22. In the first case, that of a girl of 12, pneumonectomy was recently performed; the remaining 2 cases were found in the records of the pathological museum of St. Bartholomew's Hospital, London.

The main presenting symptoms were pain in the chest in the first case, cough and pain in the chest in the second, and cough, dyspnoea with occasional chest pain, and haemoptysis in the third. The site of origin could not be determined in the first case, but the tumours in the other 2 cases were certainly hilar growths. Histologically, the tumour was undifferentiated in the first case, of predominantly oat-cell type in the second, and was of poorly differentiated mixed cellular type in the third. The author points out that this is broadly in agreement with the findings in the literature, which show a preponderance of undifferentiated growths and adenocarcinomata in children and young adults, one striking exception being a squamous-celled carcinoma in a girl of 6. *A. J. Karlish*

1383. **Prognosis in Cancer of the Lung**
K. WINGE. *Danish Medical Bulletin* [*Dan. med. Bull.*] **5**, 147–152, May, 1958. 15 refs.

The author reviews the findings in all cases seen at the Central Tuberculosis Dispensary, Copenhagen, between 1935 and 1955 in which radiological examination of the chest led to a diagnosis of bronchial carcinoma which was subsequently confirmed at operation, on biopsy examina-

tion, or at necropsy. The total number of cases was 1,102 and in all of them the course of the disease was followed to the end of 1956. Details of the age and sex distribution of the patients, the site of the tumour, symptoms and their duration in relation to operability, and the survival rates are given in tables. [For these the original paper must be consulted.] The author draws a number of conclusions from the analysis. Some 75% of the patients were referred because of symptoms " of one sort or another "; however, it was found that some of the remainder, whose condition was diagnosed only on routine mass radiological examination, had had symptoms previously, so that the total percentage with symptoms was 84. He emphasizes, therefore, that all patients with suggestive symptoms should be referred for radiological examination without delay. Bronchial carcinoma must be suspected in the large group of patients with " catarrhal symptoms ", especially those in the age group 45 to 69 years, and even if the radiograph is normal further investigation is indicated. The highest operability rate (55%) was found by " group investigations " among apparently healthy individuals, and he advocates that such investigations should be carried out " within the region of the dispensary ".

K. C. Robinson

1384. **A Comparative Study of Intrapulmonary Gas Mixing and Functional Residual Capacity in Pulmonary Emphysema, Using Helium and Nitrogen as the Test Gases**

J. B. HICKAM and R. FRAYSER. *Journal of Clinical Investigation* [*J. clin. Invest.*] **37**, 567–573, 1958. 13 refs.

At Duke University School of Medicine, Durham, North Carolina, the authors have compared the reliability of their method for measuring the functional residual capacity (F.R.C.) with an open circuit and prolonged helium clearance, in which correction for errors due to inequality of alveolar gas distribution can be made, with the standard open-circuit nitrogen wash-out method introduced by Darling *et al.* (*J. clin. Invest.*, 1940, **19**, 609), in which an alveolar sample has to be taken as representative of the mean intrapulmonary gas concentration. They give details of the widely accepted exponential analysis of clearance data employed to measure the size and contribution of the slowly ventilated portion of the lungs and the use of this analysis in estimating the F.R.C. They also give details of the allowances to be made for the amount of helium and nitrogen contributed by the body tissues in each method.

Determinations of the F.R.C. of 11 normal healthy subjects aged 21 to 29 years showed good agreement when measured by the two methods, but in 21 patients with emphysema the standard nitrogen wash-out method gave lower values than the authors' helium method. This was not due to the use of different gases, since the latter method gave the same results whether nitrogen or helium was used as the gas. The authors consider that the standard nitrogen method gives results which are too low largely because in patients with severe emphysema the alveolar air sample is not representative as a result of the defective gas mixing present in such cases.

[The authors do not mention previous work, published at various times during the last 10 years, which drew attention to these same errors in the standard technique and pointed out that the results for the F.R.C. in abnormal subjects were too low compared with those obtained by the closed-circuit techniques in frequent use in Britain and Europe.] *P. Hugh-Jones*

1385. **The Measurement of the Pulmonary Diffusing Capacity in the Presence of Lung Disease**

D. V. BATES. *Journal of Clinical Investigation* [*J. clin. Invest.*] **37**, 591–605, April, 1958. 3 figs., 35 refs.

There are some six different methods in clinical use designed to measure the " diffusing capacity " of the lung. Since the total diffusing capacity must be the average of the diffusing capacities of all the individual alveoli weighted according to the number of each with different individual diffusing capacities, the whole concept is complex. Moreover, the interpretation of measurements of the " diffusing capacity " must be even more doubtful when, as in pulmonary disease, there is a wide variation in distribution not only of the local diffusing capacity, but also of ventilation and blood flow, since this will affect the total surface area of lung available for gaseous diffusion.

In studies carried out at the Royal Victoria Hospital (McGill University), Montreal, the author has assessed the " steady state " carbon monoxide technique for measuring diffusing capacity (D_{CO}) from data on 24 normal subjects and 151 patients, some with no inequality of alveolar ventilation and some with definite inequality, as shown by the closed-circuit helium-dilution method. It was found that during exercise there was in all these subjects good correspondence between the values for D_{CO} calculated from end-tidal samples (as an estimate of mean alveolar CO concentration) and those calculated by means of the Bohr equation. Inequality of ventilation does not significantly affect this comparison. It was further shown that on exercise the rate of uptake of CO alone showed good correlation with such measurements of diffusing capacity, but that this was not so at rest, when the rate of CO uptake was greatly influenced by ventilation; thus a demonstrably abnormal diffusing capacity may exist with a relatively high rate of CO uptake.

The author analyses the results reported by other workers using other methods, and concludes that however difficult the exact interpretation of measurements of diffusing capacity may be in disease, the general results agree in regard to emphysema, diffuse interstitial pulmonary fibrosis, and sarcoidosis, even when the diffusing capacity is estimated by such different methods as the Riley technique of D_{O_2} measurement, the single-breath D_{CO}, the Filley steady-state D_{CO} (calculated from the arterial pCO as a measure of alveolar pCO), and methods using oxygen labelled with radioactive carbon. However, the steady state D_{CO} on exercise cannot be related to the D_{O_2} in cases of diffuse pulmonary fibrosis by means of the usual conversion factor, because the mean tension gradient between alveolar and capillary oxygen then appears to be impossibly large. *P. Hugh-Jones*

Urogenital System

1386. **Acute Glomerulonephritis of Childhood**
J. STEEN and R. RINVIK. *Journal of the Oslo City Hospitals* [*J. Oslo Cy Hosp.*] **8**, 88–98, May, 1958. 7 figs., 5 refs.

The authors report 153 cases of acute glomerulonephritis treated at Ullevål Hospital, Oslo, during the period 1950–56, of which 150 have been followed up. The largest number occurred during the winter months, and a history of preceding upper respiratory infection was obtained in 117 cases (sore throat 63, "catarrhal infection" 23, acute otitis 31) and of scarlet fever in only 6, while 2 were associated with "purpura rheumatica". In the majority of cases with a history of infection the nephritis developed within 3 weeks of the infection. Most of the patients were between the ages of 3 and 8 years and 89 were boys and 64 girls. In 33 cases the antistreptolysin-O titre was normal, while in 117 it rose during the first weeks to a maximum level of from 250 to over 2,000 units; it was not determined in 3 cases.

Treatment was by rest in bed, either till the urine was normal or, later in the series, until there was no macroscopic haematuria and the erythrocyte sedimentation rate was normal. The intake of fluid and protein was restricted until the blood urea level returned to within normal limits, which usually occurred within one week; (in 72 cases the blood urea level was over 40 mg. per 100 ml. on admission). All the patients were given 300,000 units of crystalline penicillin intramuscularly daily for 10 days. Every other patient among the first 86 also received an antihistaminic, but no difference in the course of the disease was observed. In 7 cases there was no proteinuria on admission; after 2 weeks only 36% still had proteinuria and after 8 weeks only 10%; in 2 cases the proteinuria was still present after 18 weeks. Haematuria persisted longer, abnormal urinary sediment counts being recorded in half the cases after 16 weeks. No patient died, and of the 144 followed up for 2 years, only 3 could not be considered completely cured. These 3 had no history of antecedent infection, oedema, or hypertension on admission, and their antistreptolysin titre was normal; the diagnosis in these cases, therefore, was not certain, but no other cause for the urinary changes could be found.

C. Bruce Perry

1387. **Use of Combined Hormone and Mechlorethamine (Nitrogen Mustard) Therapy in Lipoid Nephrosis**
C. D. WEST. *A.M.A. Journal of Diseases of Children* [*A.M.A. J. Dis. Child.*] **95**, 498–515, May, 1958. 7 figs., 34 refs.

It has been shown that adrenocortical steroids and corticotrophin (ACTH) produce a remission in some 80% of children with lipoid nephrosis, but that on withdrawal of these hormones albuminuria and oedema often recur rapidly. Long-term maintenance treatment with cortisone has been used to prevent relapse, but the condition may become resistant to such treatment, and the large doses required may produce Cushing's syndrome. Recently mustine hydrochloride (nitrogen mustard) has been given in combination with steroid treatment and found to produce a more constant diuresis and longer remissions.

Further experience of this combined treatment is reported in this paper from the University of Cincinnati College of Medicine with reference to 12 patients aged 1¼ to 6½ years with lipoid nephrosis who were followed up for periods of 6 months to 2½ years. In most cases corticotrophin was given as 80 mg. of the gel daily together with supplements of potassium and calcium, the dosage of these varying slightly with age. Mustine hydrochloride in a dosage of 0·1 mg. per kg. body weight daily was given intravenously for the last 4 days of the course of corticotrophin. Assessment of progress was based largely on the results of urinary tests for albumin carried out by the parents after instruction. Further treatment was given if albuminuria recurred, and before the onset of oedema.

Therapy produced a diuresis in all patients and, in all but 2 cases, the albuminuria disappeared. Patients who received hormone treatment for 20 or more of the 30 days before administration of mustine hydrochloride had remissions of satisfactory length, but shorter courses were less successful and preliminary hormone treatment for less than 6 days failed. In these 12 patients 15 prolonged courses of hormone treatment terminating with mustine hydrochloride resulted in remissions which were longer than those previously produced by hormones alone; of the 15 courses, 3 were of cortisone followed by corticotrophin and 12 of corticotrophin alone. Patients receiving cortisone fared better than those given ACTH only, and the author's present practice is to give 150 to 250 mg. of cortisone daily for 1 to 14 days; over the succeeding 4 days cortisone is gradually replaced by corticotrophin, and corticotrophin gel in doses of 60 to 100 mg. daily is continued alone on Days 19 to 25, the mustine hydrochloride being given in addition on Days 21, 22, 23, and 24.

It is concluded that diuresis in nephrosis is surer and remission longer if mustine hydrochloride is combined with hormone treatment, provided that the preliminary hormone treatment is given for at least 20 days. If given with care mustine hydrochloride produces only transient vomiting and occasional phlebitis. *David Phear*

1388. **Metaphyseal Decalcification of the Bone in Nephrosis, with Reference to Its Origin.** [In English]
C. HOOFT and A. VERMASSEN. *Annales paediatrici* [*Ann. paediat.* (*Basel*)] **191**, 129–146, Sept., 1958. 5 figs., 21 refs.

Endocrinology

1389. **Relationships between Clinical Severity of Hyperthyroidism and Results of Thyroid Function Tests**
A. L. SCHULTZ and L. ZIEVE. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **18**, 629–635, June, 1958. 1 fig., 6 refs.

In this study, carried out on 53 patients with unequivocal clinical hyperthyroidism at the Veterans Administration Hospital, Minneapolis, every patient was carefully questioned and examined and, in the authors' words, " a quantitative clinical severity score was derived by rating the most important symptoms and signs of hyperthyroidism on a 7-point scale, weighting the items on the basis of their clinical importance, and combining the weighted ratings to get a single score ". Nine different laboratory tests of thyroid function were then performed on each patient and the correlations between the clinical severity of the disorder and the results of individual tests and the combined tests were calculated. The tests employed were the thyroidal uptake of radioactive iodine (^{131}I) at 3 and at 24 hours, the rate of thyroidal uptake of ^{131}I, the thyroidal clearance of ^{131}I at 2 hours, the plasma content of protein-bound ^{131}I at 24 hours, the conversion ratio at 24 hours, the chemically determined serum protein-bound iodine level, the basal metabolic rate (B.M.R.), and the serum total cholesterol level. The conclusion was reached that two tests alone, namely, the thyroidal clearance of ^{131}I and the B.M.R., were as effective as all the tests together in predicting the clinical severity of hyperthyroidism. *G. B. West*

1390. **Gross Digital Clubbing and Exophthalmic Ophthalmoplegia in Thyroid Disorders**
A. G. FREEMAN. *Lancet* [*Lancet*] **2**, 57–60, July 12, 1958. 4 figs., 20 refs.

In a study of the literature the author has found 6 reports of cases in which exophthalmos and digital clubbing occurred in the same patient, and in 4 of these the ophthalmopathy was classed as exophthalmic ophthalmoplegia; this association occurred both in hypothyroid and in euthyroid individuals. From the Royal Infirmary, Bristol, he now reports another 2 patients in whom there appeared to be a coincidental onset of exophthalmic ophthalmoplegia and clubbing of the fingers, and in whom no cardiac, pulmonary, hepatic, or familial disorder was present. One of these patients was hypothyroid, while the other showed what the author claims is the unique association of progressive exophthalmos, clubbing of the fingers, and hyperthyroidism.

Since progressive exophthalmos is thought to be a manifestation of pituitary dysfunction, the association of finger clubbing in these cases raises the question whether the latter condition might have a similar endocrinological basis. In support of this thesis the author cites the necropsy findings in 2 patients with hypothyroidism, exophthalmic ophthalmoplegia, pretibial myxoedema, and gross digital clubbing in whom eosinophil hyperplasia of the anterior lobe of the pituitary gland was also present. *D. G. Adamson*

1391. **The Action of Fludrocortisone and Aldosterone on Sodium and Potassium Metabolism in Addison's Disease**
D. S. MUNRO. *Clinical Science* [*Clin. Sci.*] **17**, 205–216, 1958. 6 figs., 29 refs.

It has been shown that the administration of cortisone acetate to patients with Addison's disease previously treated with implants of deoxycortone acetate may be followed by a loss of sodium from the body. Since the onset and duration of action of deoxycortone acetate cannot be precisely predicted, however, the effect of cortisone acetate on sodium retention resulting from a standard course of treatment with the potent sodium-retaining cortico-steroid fludrocortisone was investigated at the Royal Infirmary, Sheffield, in 7 patients with Addison's disease, all of whom were being maintained solely on cortisone acetate and had not received implants of deoxycortone acetate for at least 2 years. So far as possible dietary and environmental conditions were kept constant, and the patients remained ambulant throughout the period of study.

When these patients were given 0·5 mg. of fludrocortisone by mouth per day there was invariably an increase in both the serum sodium level, measured by flame photometry, and in the amount of exchangeable sodium, measured by means of radioactive isotopes. The administration of cortisone acetate (in doses up to 100 mg. per day) together with fludrocortisone did not significantly affect the response to administration of fludrocortisone alone. It was observed that fludrocortisone caused greater sodium retention when the serum sodium level was low. Observation of one patient given aldosterone showed that this substance had no definite effect on either exchangeable sodium or potassium, or on the serum levels of these salts, although the same patient did respond to fludrocortisone. Fludrocortisone caused a slight fall in the serum potassium level, but had no effect on exchangeable potassium. *P. A. Nasmyth*

1392. **Observations of Plasma and Urinary Steroid Levels following the Administration of Zinc–ACTH and Gel-ACTH**
S. C. SIEGEL, B. J. LOVIN, R. SMITH, R. S. ELY, and V. C. KELLEY. *Annals of Allergy* [*Ann. Allergy*] **16**, 252–267, May–June, 1958. 5 figs., bibliography.

The authors have investigated the potency and duration of action of two repository preparations of corticotrophin (ACTH), one a suspension in zinc hydroxide and the other in the form of a gel. To 10 normal healthy subjects 40 or 80 units of either zinc–ACTH or ACTH gel was given intramuscularly and the effect of these substances on the plasma 17-hydroxycorticosteroid

concentration, the urinary 17-hydroxycorticosteroid and 17-ketosteroid excretion, and the eosinophil response studied.

The plasma steroid concentration was increased for 16 hours after ACTH gel and for 24 hours after zinc–ACTH. This difference was not reflected in the urinary excretion of steroids, while the eosinophil response reflected the difference in some tests only. The maximum increase in plasma steroid concentration was the same whether 40 or 80 units of ACTH was given. In contrast, the urinary excretion of steroids following 80 units of ACTH gel was definitely greater than that following 40 units.

H. Herxheimer

DIABETES

1393. **Results of Long-term use of Tolbutamide (Orinase) in Diabetes Mellitus**

H. Mehnert, R. Camerini-Dávalos, and A. Marble. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **167**, 818–827, June 14, 1958. 7 figs., 16 refs.

This paper analyses experience gained during a period of 21 months in the administration of tolbutamide to 1,030 diabetic patients at the Joslin Clinic and New England Deaconess Hospital, Boston, and at two summer camps for children. The majority of the patients were over the age of 40 years and required less than 40 units of insulin a day for stabilization. Between 1 and 3 g. of tolbutamide was given daily, either in a single dose at breakfast time or in 2 doses, one at breakfast and one at supper. Gastric irritation was avoided by giving the drug with meals.

Of the 1,030 patients, 227 who received a single test dose only, 21 for whom insufficient data were available, and 10 who were treated with a combination of insulin and tolbutamide were excluded from the present study, which is primarily concerned with the remaining 772 patients who started regular treatment with tolbutamide. This was stopped within one month because of poor results in 136 cases (17·6%), owing to toxic effects in 5, and for non-medical reasons in 4, while 33 patients (4·3%) responded well, but were followed up for less than a month. Of the 594 cases (76·9%) in which treatment was continued for one to 20 months, good control was considered to be achieved with tolbutamide in 407 (52·6%) and fair control in 143 (18·5%), these degrees of control being defined in terms of blood and urine sugar levels at various intervals after meals; in 31 cases (4·0%) a good response was obtained initially, but was not maintained, and in 9 others treatment failed because of dietary negligence; one patient stopped treatment for non-medical reasons and 3 because of side-effects. Thus in only 8 (1·1%) of 772 cases had treatment to be discontinued on account of toxic effects, which consisted in allergic rashes in 4 cases and various symptoms (of questionable relationship to the drug) in the others. There was no case of leucopenia. During the period of study 12 patients died, 7 of them of myocardial infarction. In 2 cases in which a post-mortem examination was made there was no evidence of pancreatic or hepatic damage attributable to tolbutamide.

Good control was observed more often in cases in which the onset of diabetes was late and in those in which the previous dosage of insulin was low. The authors suggest that observation of the response of the blood sugar level to a single dose of tolbutamide (the sulphonylurea response test) is of value in predicting probable failure to achieve control with the drug, but is less reliable for the selection of those patients in whom long-term treatment may be expected to be successful. A table, based on correlation of the result of the test with the fasting blood sugar level and the subsequent response to treatment in 240 cases, gives the standard values recommended for use in interpreting the test result.

Charles Rolland

1394. **Oral Treatment of Diabetes. Trial of Phenethyldiguanide (D.B.I.)**

G. H. Hall, M. F. Crowley, and A. Bloom. *British Medical Journal* [*Brit. med. J.*] **2**, 71–74, July 12, 1958. 2 figs., 16 refs.

A clinical trial of phenethyldiguanide (N-β-phenethylformamidinyl iminourea; D.B.I.) was carried out on diabetic patients at the Whittington Hospital, London. This drug has previously been shown to be capable of reducing the blood sugar content in animals even in the absence of endogenous insulin. The 40 patients studied ranged in age from 18 to 78 (average 57) years, and in 14 of them diabetes was newly diagnosed and untreated. All were admitted to hospital, and after an observation period of one week, if possible under dietary control alone, they were given a single dose of 150 mg. of D.B.I. by mouth and the blood sugar level estimated at 2-hourly intervals for the next 12 hours. On subsequent days 50 mg. was given 3 times daily before the main meals. The full course of treatment lasted 6 weeks, the blood sugar level being estimated each day at noon, before lunch.

The hypoglycaemic response to the single dose was variable, but generally reached a maximum in 6 hours and disappeared after 10 hours. In about one-third of the cases no effect was observed. Continued treatment produced a progressive fall in blood sugar level up to the sixth day, the mean blood sugar level for the group then being 60% of the mean pretreatment level. Glycosuria fell in parallel with the blood sugar level. In 5 cases in which tolbutamide had been ineffective the patient responded to D.B.I. Ketosis was completely unaffected by the drug. In one case, although the blood sugar level fell to normal and sugar was no longer present in the urine, the ketosis increased; on withdrawal of the drug glycosuria and hyperglycaemia reappeared, but the ketosis diminished. No effect could be demonstrated on the plasma inorganic phosphorus or amino-acid nitrogen content. Gastro-intestinal side-effects occurred in 26 cases and were of such severity that these patients could not complete the planned course of 6 weeks. No skin rashes or blood dyscrasias were noted.

The authors conclude that the side-effects of the drug and its failure to prevent ketosis preclude its general clinical use, but it is clearly a drug of considerable physiological interest.

T. D. Kellock

The Rheumatic Diseases

1395. **Relation between C-reactive Protein and Erythrocyte Sedimentation Rate in Rheumatic Fever**
R. ROZANSKY and E. DAVIS. *American Journal of Clinical Pathology* [*Amer. J. clin. Path.*] **29**, 331–333, April, 1958. 1 fig., 11 refs.

The authors report, from the Rothschild–Hadassah University Hospital, Jerusalem, a study of the C-reactive protein (C.R.P.) content of the serum and the erythrocyte sedimentation rate (E.S.R.,) (Westergren) in 448 patients (adults and children) with rheumatic fever or rheumatic heart disease, 700 specimens of blood being examined. There was a well marked correlation between the results of the two estimations. The discrepancies, however, were informative. C.R.P. was present in 15% of the specimens showing a normal E.S.R. In specimens of blood from 9 patients with active rheumatic fever and congestive heart failure the reaction to the C.R.P. test was strongly positive and the E.S.R. was normal. The response to the C.R.P. test was negative in 40% of specimens showing an E.S.R. between 21 and 50 mm. in 1 hour, probably because C.R.P. usually disappears from the serum before the E.S.R. reaches normal levels.

In 5 out of 22 pregnant women suspected of having rheumatic activity the result of the C.R.P. test was negative although the E.S.R. was above 50 mm. in one hour. The authors consider that in such cases rheumatic activity could probably be excluded, since a number of workers have found that during normal pregnancy the E.S.R. is usually raised, but the response to the C.R.P. test is positive in only 17 to 32% of cases.

E. G. L. Bywaters

1396. **The Serum Mucoprotein Content as a Diagnostic Index and a Measure of Activity in Rheumatic Fever in Children.** (Le mucoproteine quale indice diagnostico e di attività della malattia reumatica in pediatria)
M. QUARTI, M. TARANTINO, and E. VASSENA. *Ospedale maggiore* [*Osped. maggiore*] **46**, 95–101, March [received May], 1958. 23 refs.

This paper from the University of Milan reports the results of the estimation of serum mucoprotein levels in 98 patients with rheumatic fever. The technique of estimation is given in detail. Of these 59 male and 39 female patients, ranging in age from 4 to 13 years, 74 were in-patients at the Ospedale Maggiore of Milan, and in these the estimations were performed before treatment with prednisone or phenylbutazone and repeated after recovery. The other 24 children were apparently well, but had a history of previous rheumatic fever.

In many cases the serum mucoprotein level was raised during the acute phase of the disease, but tended to become normal later. Very high levels were often associated with a markedly raised erythrocyte sedimentation rate. It is concluded that an increase in the serum mucoprotein level is of diagnostic value, but is not an absolute expression of the activity of rheumatic fever.

David Friedberg

CHRONIC RHEUMATISM

1397. **Experience in the Management of Joint and Soft Tissue Disease with a New Form of Hydrocortisone for Local Injection**
E. L. COODLEY. *Journal of Chronic Diseases* [*J. chron. Dis.*] 7, 429–439, May, 1958. 23 refs.

The author first briefly reviews some of the literature on the treatment of disease of the joints and bursae by intra-articular injection of steroid compounds and then reports results obtained at the Cedars of Lebanon Hospital, Los Angeles, with concentrated preparations of hydrocortisone, 150 or 200 mg. of this steroid in 1 ml. being the usual dose injected into the joints. The 56 patients studied were suffering from various diseases, including rheumatoid arthritis, osteoarthritis, gout, bursitis, and tenosynovitis. In most cases the lesions were chronic and other forms of treatment had already been tried, while in some it was possible to compare the effect of the new treatment with the results obtained with the more usual smaller doses of hydrocortisone (50 mg. per ml. injected locally).

The results, which were evaluated subjectively, by clinical examination, and in a few cases by study of C-reactive protein reactions, showed that the over-all incidence of improvement resembled that obtained with the injection of the usual doses of steroids. Certain joints, however, showed unusually good results, improvement being noted in all elbows treated, 87% of knees, 83% of ankles, and 73% of shoulders. The benefit obtained was also of longer duration, improvement lasting 11 days or more in 40%, as compared with 30% of the cases given the lower doses of steroids. Side-effects of steroid therapy, both local and systemic, occurred but were minimal. The author concludes that concentrated intra-articular injections of hydrocortisone produce somewhat better results than conventional doses, especially in resistant cases of tenosynovitis, chronic bursitis of the shoulder and elbow, and post-traumatic lesions.

M. Kendal

1398. **Laryngeal Stridor in Rheumatoid Arthritis**
C. S. DARKE, L. WOLMAN, and A. YOUNG. *British Medical Journal* [*Brit. med. J.*] **1**, 1279–1282, May 31, 1958. 7 figs., 24 refs.

The authors describe 5 cases of laryngeal stridor associated with advanced rheumatoid arthritis seen at the Royal Infirmary and the City General Hospital, Sheffield. In 4 instances the stridor was so severe that tracheotomy was necessary.

In the first case, that of a man aged 62 who had suffered from rheumatoid arthritis for 5 years, an emergency tracheotomy was required in order to relieve an obstruction of the respiratory tract. Signs of bilateral abductor paralysis of the larynx were revealed on laryngoscopy; the cricoarytenoid joint movements were

unrestricted. Diffuse interstitial fibrosis of the lungs developed and the patient died suddenly from bronchopneumonia. At necropsy the cricoarytenoid joints were found to be fully mobile. Microscopical examination showed chronic inflammation of the subhyoid bursa and also of the synovial lining of the cricoarytenoid and cricothyroid joints. There was evidence of demyelination of the vagus and laryngeal nerves. At necropsy in another case the vagus and superior laryngeal and recurrent laryngeal nerves showed demyelination with varicose swelling of the axis cylinders. These changes were attributed to ischaemic neuritis which had resulted from a rheumatoid type of arteritis of the vasa nervorum. No signs of polymyositis or focal disease were detected in the laryngeal muscles and there was no evidence of pressure palsy.

It is suggested that when laryngeal stridor occurs in rheumatoid arthritis the condition may be produced either by arthritis of the cricoarytenoid joints or by abductor paralysis due to nerve degeneration. Cases described in the literature have a common pattern, with the onset of obstruction of the respiratory tract in the 6th or 7th decade, but the exact cause of the stridor can be established only by histological examination.

A. Garland

1399. **Interaction of the Rheumatoid Factor with Antigen–Antibody Complexes and Aggregated Gamma Globulin**
G. M. EDELMAN, H. G. KUNKEL, and E. C. FRANKLIN. *Journal of Experimental Medicine* [*J. exp. Med.*] **108**, 105–120, July 1, 1958. 5 figs., 21 refs.

The authors report a series of experiments undertaken at the Rockefeller Institute for Medical Research, New York, in an attempt to characterize further the intricate interactions between purified rheumatoid factor (R.F.) —now known to be a γ globulin with a sedimentation constant of 19 S—and antibodies and other γ globulins.

The isolation of R.F. from euglobulin fractions or precipitates obtained from the serum of 4 patients with rheumatoid arthritis is described, density gradient zone centrifugation being used to obtain 90% of the 19-S material. Evidence was obtained that the addition of purified R.F. increased the amount of precipitate formed in systems consisting of ovalbumin, human albumin, and human γ globulin with the corresponding rabbit antibodies, the precipitates being compared by determining their nitrogen content. Furthermore, an additional precipitate occurred on the addition of R.F. to the supernatant fluid removed after precipitation had taken place in the control series, indicating the reaction of R.F. with soluble antigen–antibody complexes. In the zone of excess antibody globulin, where there is no soluble antigen–antibody complex, no precipitation occurred as a result of the addition of R.F. No similar increase in precipitation by R.F. was noted in a horse anti-pneumococcus Type-III system. Heating R.F. to 56° C. for one hour reduced only slightly the potentiation of precipitation in an anti-human-albumin system, and prolonging the reaction time of the antigen–antibody system from 24 hours to 7 days at 4° C. had no significant effect. An approximate linear relationship was established between the nitrogen content of the precipitate produced by the addition of R.F. and the quantity of protein nitrogen in the antibody–antigen system.

Direct precipitation reactions occur between R.F. and heated γ globulin, this increased reactivity being known to be due to the aggregation of globulin complexes. An increase in reactivity of a similar nature was obtained by pre-treating the γ globulin with guanidine or a mixture of urea and mercaptoethanol, the effect of the latter being largely blocked by iodacetamide. Increased inhibition of the sheep-cell agglutination reactions was achieved by pre-treatment of Fraction-II γ globulin by similar methods. Zone ultracentrifugation in a sucrose density gradient demonstrated that the activity in each of these preparations was due primarily to aggregated material with a sedimentation constant greater than 20 S. Insoluble denatured precipitated human γ-globulin preparations were found to adsorb R.F., which could be readily eluted from them in urea or acid buffers, the eluate containing 70% of a 19-S component.

The authors discuss their findings and conclude that they contribute little to the solution of the question whether R.F. is an antibody to γ globulin or a complement-like substance. All the evidence indicated that only large complexes with a sedimentation constant greater than 20 S were involved in interactions with R.F. The suggestion is made that R.F. might represent an antibody to an antigen–antibody complex. *Harry Coke*

1400. **Characterization of the "Reactant" (Gamma Globulin Factor) in the F II Precipitin Reaction and the F II Tanned Sheep Cell Agglutination Test**
C. L. CHRISTIAN. *Journal of Experimental Medicine* [*J. exp. Med.*] **108**, 139–157, July 1, 1958. 13 figs., 22 refs.

An investigation is reported from Columbia University College of Physicians and Surgeons and the Presbyterian Hospital, New York, into the nature of the γ-globulin component, or "reactant", which interacts in precipitin and haemagglutination reactions with the rheumatoid factor. This factor is itself a γ-globulin complex with a sedimentation constant of 19 S, and exists in the serum of patients with rheumatoid arthritis as a soluble complex with a 7-S γ globulin, the combination having a sedimentation constant of 22 S. The complex interacts in a number of "diagnostic" tests with the γ globulin of Cohn's Fraction II (F II).

In the present investigation commercial pooled human F II was divided by precipitation with sodium sulphate (0·36 to 1·18 M) into 6 fractions, labelled SS_1 to SS_6. In the ultracentrifuge SS_1 gave a curve with an asymmetrical peak at a sedimentation constant of approximately 40 S, and SS_2 showed a fairly symmetrical component with a value of 30 S, while the remaining fractions contained no component heavier than 7 S. The hexose:nitrogen ratios of the fractions did not differ significantly from that of whole F II. Fractions SS_3 to SS_6 were heated to 63° C., after which they contained components heavier than 7 S.

In combination with rheumatoid sera Fractions SS_1 and SS_2 yielded large amounts of precipitate, which were even greater after the fractions had been heated, whereas

Fractions SS_3 to SS_6 did not produce more precipitate than was formed spontaneously in the serum. The precipitin reactivity of whole F II was intermediate between those of the inactive fractions SS_3 to SS_6 and the strongly reactive fractions SS_1 and SS_2. The separated 30-S and 40-S components alone induced precipitation with rheumatoid sera. After precipitation the supernatants were shown to contain some 22-S material which could be progressively precipitated by the addition of more SS_1, the haemagglutination titre being reduced in parallel with the removal of the precipitate. The 7-S globulin isolated was demonstrated to have an inhibitory effect on these precipitin reactions, which probably accounts for a number of phenomena observed in precipitin reactions with whole F II. Fractions SS_1 and SS_2 strongly inhibited a positive F-II–tanned-cell agglutination system, as did whole F II, though to a lesser degree. Similarly, when Fractions SS_1 and SS_2 were used to coat or sensitize sheep erythrocytes a relatively low concentration was found to be effective; incomplete sensitization was effected with SS_3, and no sensitization was obtainable with SS_4 to SS_6.

The " reactant " appears therefore to consist of molecular aggregates of γ globulin with sedimentation constants above 7 S and as high as 40 S. *Harry Coke*

1401. **16α-Methyl Corticosteroids. A New Series of Anti-inflammatory Compounds; Clinical Appraisal of Their Antirheumatic Potencies**

E. W. BOLAND. *California Medicine* [*Calif. Med.*] **88**, 417–422, June, 1958. 1 fig., 14 refs.

Over the past few years many attempts have been made to produce synthetic steroid compounds which retain their anti-inflammatory action but are free from the properties inducing deleterious physiological effects. Recently, a family of four hydrocortisone analogues with a methyl group at the 16α carbon position of the steroid nucleus have been synthesized, and on biological testing were found to possess markedly enhanced anti-inflammatory action unassociated with disturbance of electrolyte metabolism.

These four compounds, 16α-methyl-9α-fluoroprednisolone (MK–125), 16α-methyl-9α-fluorohydrocortisone (MK–126), 16α-methylprednisolone (MK–110), and 16α-methylhydrocortisone (MK–117), were tried in the treatment of patients suffering from rheumatoid arthritis, and preliminary observations are reported in this paper from St. Vincent's Hospital, Los Angeles. The selection of patients was limited to those whose maintenance dose of prednisolone was well established and stable, but who had sufficient residual evidence of active joint inflammation to permit measurement of any changes. Treatment was given with first one drug and then another, and the dosage of each drug required to maintain equivalent clinical improvement, as judged subjectively and objectively, was determined. At least two cross-comparisons were made in every case. The approximate differences between the compounds were: MK–125 was 7 times and MK–126 3 times more potent than prednisolone; the potency of MK–110 was only one-third greater than that of prednisolone; and the potency of MK–117 was only two-thirds that of prednisolone. None of these steroids caused signs of salt and water retention. The author states that the findings are in accord with the results of experiments in animals.

These preliminary observations indicate that MK–125 is the most effective anti-rheumatic agent so far produced, satisfactory control of the disease being achieved with a daily dosage of 0·6 to 2·8 mg. for periods up to 4 months. The author points out, however, that further prolonged observation is required before its value and potential hazards can be assessed.

It is concluded that the substitution of a methyl radical at the 16α position intensifies the anti-rheumatic action of certain 11-hydroxycorticosteroids.

B. M. Ansell

1402. **Increasing the Effectiveness of Gold Therapy in Rheumatoid Arthritis**

R. T. SMITH, W. P. PEAK, K. M. KRON, I. F. HERMANN, R. A. DELTORO, and M. GOLDMAN. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **167**, 1197–1204, July 5, 1958. 2 figs., 18 refs.

As part of a study at the Benjamin Franklin Clinic, Philadelphia, of the variable response to gold therapy in rheumatoid arthritis, the urinary secretion of gold was assayed on 138 occasions in a series of patients who had been given intramuscular injections of aurothioglucose and gold sodium thiomalate in a total dosage of 820 to 1,070 mg. in 24 weeks. Among patients who experienced a remission of arthritis approximately one-seventh of the dose of gold salt was excreted during the first week of administration, but among patients who showed intolerance the amount excreted was less than one-seventh of the dose. There was an approximate correlation between the total amount of gold salt administered, the excretion rate, and the onset of toxicity. Toxic reactions included pruritis, dermatitis, stomatitis, leucopenia, and disturbances of renal function. In one patient dermatitis developed after a total dose of 70 mg. of aurothioglucose had been given, while in another the skin reaction did not appear until 820 mg. had been administered. In cases of hyperretention of gold a total dose of 300 to 500 mg. had been administered before the onset of toxic reactions.

For the management of toxic reactions the authors advocate the omission of gold therapy and administration of prednisolone or prednisone in a daily dosage of 10 to 20 mg. If a rash occurs a steroid lotion may be applied locally. Dimercaprol is required only occasionally. From two-thirds to three-quarters of the previously planned dose of the gold salt should be instituted as maintenance therapy 2 to 3 weeks after the reaction has subsided and the steroid has been withdrawn. Before each injection an examination should be carried out for signs of irritation, rash, or soreness of the mouth, and the blood and urine should be examined. Every 4 weeks the laboratory tests should include a complete blood count and determination of the erythrocyte sedimentation rate.

A comparative study of the effects of gold therapy in two groups of patients showed that an " individualized " regimen was more effective than a standard regimen and

induced a remission in 82% of cases. With adequate therapy a remission can be expected in 12 to 18 weeks, and is likely to persist with maintenance therapy for an average period of 8 months. *A. Garland*

1403. **Gold in the Treatment of Rheumatoid Arthritis**
L. M. LOCKIE, B. M. NORCROSS, and D. J. RIORDAN. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **167**, 1204–1207, July 5, 1958. 7 refs.

Since 1940 at the General Hospital, Buffalo, N.Y., gold salts have been given to all patients with reversible rheumatoid arthritis who were otherwise in good health. The majority of the 369 patients received gold sodium thiomalate, but a few were given aurothioglucose. The gold salt was administered intramuscularly at weekly intervals, beginning with a dose of 10 mg., then 20 mg., and then 40 mg. weekly until a total of 500 mg. had been given. Thereafter the dosage was determined on the basis of the clinical status of the patient. The injection was given into the deltoid muscle, a 24-gauge ¾-inch (19·1-mm.) needle being used. There were no local inflammatory reactions with this technique.

Compared with a group of 566 controls the patients given gold salts had " a 20% better chance of complete recovery or major improvement ". Favourable results were obtained in a relatively large number of patients suffering from moderate or severe rheumatoid arthritis, and the authors suggest this good response was due to close observation and treatment extending over a period of many months or years. A total dose of more than 300 mg. of the gold preparation was required in order favourably to influence the course of the disease. Severe side-effects were few, since care was taken to observe " the warning appearance of glossitis and dermatitis ". The reactions were controlled by omitting gold treatment and administering antihistaminics, steroids, and dimercaprol when necessary. It is emphasized that although evidence of sensitivity to gold salts may appear at any time, the treatment can be continued for years without precipitating a reaction, provided there is careful and constant observation of the patient for signs of such sensitivity. In 50% of patients with mild reactions treatment can be continued, although the dosage may have to be reduced. *A. Garland*

1404. **Long-term Treatment of Rheumatoid Arthritis with Mepacrine and Chloroquine.** (Langtidsbehandling af rheumatoid arthritis med mepacrin og chloroquine)
F. ERLENDSSON. *Ugeskrift for Læger* [*Ugeskr. Læg.*] **120**, 793–799, June 19, 1958. 18 refs.

The author reports the results obtained with mepacrine and chloroquine in the long-term treatment of 14 patients (11 women) with rheumatoid arthritis. All but 4 of the patients were over 50 years of age, and in 6 of them the onset of the illness had taken place at least 20 years previously. Except for one patient all had disease graded as Stage II, III, or IV. The minimum daily dose of mepacrine was 100 mg., and that of chloroquine diphosphate 250 mg.

In 7 patients who were followed up for 1½ to 3 years the severity of the condition lessened by one or two grades, while 2 others discontinued active treatment in view of their continued well-being. Toxic reactions made withdrawal of the drug necessary in 5 patients, 4 of these developing cardiac pain and one a rash. In 3 cases chloroquine was substituted for mepacrine without a break in therapy. Although no conclusions are reached regarding the type of case most suitable for this therapy, the author is convinced of the value of chloroquine in the treatment of rheumatoid arthritis. It is of interest that two patients who had failed to respond to cortisone showed marked improvement with the antimalarial drugs. Several detailed case histories are presented.
H. F. Reichenfeld

1405. **The Treatment with Chloroquine of 20 Patients with Active Rheumatoid Arthritis.** (Chloroquinebehandling af 20 patienter med aktiv rheumatoid arthritis)
F. ERLENDSSON. *Ugeskrift for Læger* [*Ugeskr. Læg.*] **120**, 800–804, June 19, 1958. 11 refs.

The treatment with chloroquine of 16 female and 4 male patients suffering from active rheumatoid arthritis is described. Their ages ranged from 24 to 71 years and, with the exception of a 57-year-old woman in Stage IV, the disease in the others was in Stages I, II, or III. Previous methods of treatment had included gold therapy in 5 cases and corticosteroid therapy in 8. Chloroquine therapy was started with a daily dose of from 500 to 750 mg. of the diphosphate, this being reduced to 250 to 500 mg. daily when either the onset of side-effects made it necessary or a good therapeutic response had been obtained.

After a period of treatment which in most cases lasted from 2 to 6 weeks 5 patients had a complete remission, 10 showed major and 3 minor improvement, and 2 were not improved. In 10 cases the treatment was continued for further periods ranging from 80 to 700 days, and by this time the disease in 6 patients had regressed to Grade I and in the remaining 4 to Grade II. Similar assessment in another 6 cases, which responded to the initial course of treatment but in which chloroquine therapy had been discontinued, showed improvement to Grade I in 4 cases and to Grade II in 2.
H. F. Reichenfeld

1406. **The Treatment of Rheumatoid Arthritis with Premaquine and Chloroquine.** (Behandling af rheumatoid arthritis med primaquine–chloroquine)
F. ERLENDSSON. *Ugeskrift for Læger* [*Ugeskr. Læg.*] **120**, 804–809, June 19, 1958. 23 refs.

Detailed case histories are presented of 6 patients with active rheumatoid arthritis who were treated with an intensive course of antimalarial drugs at the Amtssygehus, Aarhus, Denmark. This consisted in the administration of chloroquine diphosphate, 500 mg. three times daily, and primaquine phosphate, 7·5 mg. of the base, twice daily. Side-effects, in the form of diarrhoea, giddiness, sweating, and nausea, were so severe that after 5 days treatment of one patient was stopped, while the 5 others continued on a much reduced dosage for further periods of 11 to 60 days. On cessation of treatment 2 of these patients showed improvement to Grade III and 3 to Grade II. *H. F. Reichenfeld*

Physical Medicine

1407. **Bilateral Effects of Unilateral Exercise: Experimental Study Based on 120 Subjects**
R. D. KRUSE and D. K. MATHEWS. *Archives of Physical Medicine and Rehabilitation* [*Arch. phys. Med.*] **39**, 371–376, June, 1958. 3 figs., 19 refs.

There is no general agreement that exercise of one limb can lead to cross-transfer of strength to the opposite unexercised limb. A review of the literature has shown that the results of investigations carried out so far are inconclusive and that those workers who claim to have observed cross-transfer of strength give widely different reasons for their findings.

The present authors report a controlled investigation on 120 male university students, 60 of whom constituted a working group and 60 a control group. The working group was divided into four subgroups, each of 15 individuals, the subgroups "working" on 2 days, 3 days, 4 days, and 5 days each week respectively. The work consisted in lifting a weight by using the left elbow flexors, an ergometer being employed both to exercise the muscles and to measure endurance in terms of the total distance the load was raised during the test period. The right elbow flexors were tested against the left elbow flexors at the beginning and end of a 4-week period. The control group was matched with the exercised group, and was tested at the beginning and end of the 4-week period without being exercised in the interval.

Statistical analysis of the results showed that in the exercised groups there was a significant increase in strength of the exercised flexors in those subjects who worked on 3, 4, or 5 days each week, but not in those who worked on 2 days a week. There was no evidence of any increase in strength of the opposite unexercised flexor muscles or in any of the muscles of the controls.

W. Tegner

1408. **Physical Therapeutic Measures in the Treatment of Chronic Bronchopulmonary Disorders. Methods for Breathing Training**
W. F. MILLER. *American Journal of Medicine* [*Amer. J. Med.*] **24**, 929–940, June, 1958. 3 figs., bibliography.

The physical measures, other than drug therapy, that may be of considerable help in the treatment of chronic bronchitis, bronchiectasis, and bronchial asthma associated with chronic pulmonary emphysema are discussed in some detail in this paper from the University of Texas Southwestern Medical School, Dallas. The major respiratory difficulty in these disorders lies in the obstruction to the expiratory flow of air, which in turn causes air-trapping and over-distension of the alveolar sacs—a sequence of events which may cause only slight discomfort at rest, but which becomes pronounced on exertion. Over-distension gives rise reflexly to: (1) further increase in the work of breathing; (2) elevation of the thorax in the respiratory mid-position; (3) an increase of the functional residual ventilation; and (4) because of the additional factor of diminished pulmonary elasticity, to premature expiratory collapse of the bronchi or bronchioles. A vicious circle is thus created which can be broken only by relief of the obstruction.

The main measures are as follows. (1) Muscular relaxation, the success of which depends upon individual attention by the physician and physiotherapist. Optimum relaxation before a training session may be assisted by use of a bronchodilator drug and oxygen inhalation through a mask, a catheter, or intermittent positive-pressure apparatus according to requirements. (2) Inculcation of the habit of quiet abdominal–diaphragmatic breathing to bring about increased elevation of the diaphragm in expiration and deflation of the lungs. Although expiratory dominance is not the normal rhythm of respiration the author believes that this exercise [effective in his hands] is of value in impressing upon the patient the importance of emptying his lungs well before each inspiration. The need for postural drainage before exercises in some cases and the use of intermittent positive-pressure breathing during them in others is emphasized. [Intermittent positive-pressure machines are a common sight in most chest hospitals in the U.S.A. and without doubt are most valuable in selected cases.] (3) Breathing through pursed lips is beneficial, in the author's opinion, in that it places the obstruction above bronchial level and so causes an increase in pressure within the airways which tends to diminish their premature expiratory collapse; it should be combined with the other exercises. (4) Decompression exercises, in which the arms are folded about the lower part of the chest to assist in more complete expiration, are taught when the previous manœuvres have been mastered; they are combined with successive quick expiratory efforts.

The author places great emphasis on carefully supervised graduation of the patient from these various exercises at rest to walking and other forms of activity, and urges the need for continual and vigorous practice by the patient who, when he becomes breathless, should at once direct his attention to abdominal–diaphragmatic breathing. The wearing of an abdominal belt and the induction of pneumoperitoneum may be valuable in some cases, particularly in those patients who are unable to develop control of the abdominal musculature or who have a chronic bronchopulmonary infection.

In conclusion, in refuting some recent criticism which has suggested that such exercises are of dubious value, the author states that when treatment has been properly established respiratory function tests such as those of maximal breathing capacity and vital capacity may show no major change, although the patient is obviously breathing more easily both at rest and on exercise. He again stresses the need for initial rigorous training for at least 3 months, and for exercises indefinitely.

[There is a need for such methods to be applied on a large and organized scale in Great Britain for this type of patient, and the space, at least, is now available in sanatoria.] *Raymond Parkes*

Neurology and Neurosurgery

1409. **Disturbed Relaxation of Limbs**
S. BEHRMAN. *British Medical Journal* [*Brit. med. J.*] **1**, 1454–1457, June 21, 1958. 7 refs.

The author describes certain motor and sensory disturbances in the limbs, chiefly the legs, which appear only when the limbs are relaxed or during sleep. The onset is in early adult life, but the disorder persists for many years with considerable fluctuation. Cases fall into 5 groups according to the nature of the main symptoms. In the myoclonus group there is a localized muscular contraction, with or without movement of the limb, limited to the legs and occurring during relaxation; on different occasions different muscle groups are affected. In a second group aching, gnawing, or throbbing pains in the relaxed limbs mount in severity and culminate in myoclonus, while in a third group there is pain without myoclonus during waking hours, although myoclonus is commonly present during sleep. (The author points out that myoclonus during sleep is common to all 5 groups.) In a fourth or " sleep-pain " group the onset of symptoms after relaxation is delayed for hours; pain may wake the patient in the night but often it is felt only immediately on waking in the morning. A fifth group is characterized by crural sensations " defying description " and restlessness of the limbs, the symptoms occurring only at rest.

This disturbed relaxation of limbs is often familial and may be aggravated by pregnancy or anaemia. In most cases symptoms are appreciably relieved by phenobarbitone. The author suggests the term " dyslysis " for this syndrome. *Hugh Garland*

1410. **Sensory Nerve Action Potentials in Patients with Peripheral Nerve Lesions**
R. W. GILLIATT and T. A. SEARS. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] **21**, 109–118, May, 1958. 8 figs., 7 refs.

In the determination of nerve action potentials in normal subjects and in patients with suspected peripheral nerve lesions examined at the National Hospital, Queen Square, London, the authors used Dawson's modification of his own technique (*J. Physiol.* (*Lond.*), 1956, **131**, 436) in which the digital sensory nerves are stimulated electrically with single shocks through ring electrodes wrapped round the fingers and the action potential of the afferent volley recorded through surface electrodes placed over the median or ulnar nerves just above the wrists.

In healthy control subjects (67 observations) the afferent volleys recorded at the wrist varied considerably in amplitude in different individuals, and little significance was therefore attached to small variations in amplitude in the tests on patients, in whom, however, increase in the latent period of appearance of the action potential at the wrists was sometimes helpful in detecting the presence of a damaged nerve. Of 41 patients with a suspected lesion of the median or ulnar nerve, no sensory action potential could be recorded from the affected nerve in 13. In the remainder the recorded action potentials were of small amplitude and increased latency compared with those of the controls. In 2 patients with brachial plexus lesions and sensory loss in the hand no sensory action potentials could be recorded. In 7 patients with chronic polyneuritis and 2 with peroneal muscular atrophy sensory action potentials were both small and delayed in 2 cases and absent in the other 7. The site of the nerve lesion in the arm was of importance; thus in patients with median neuritis at the wrist the segment of nerve examined included the damaged portion, and this enabled a high proportion of mild cases to be recognized. In the case of lesions of the ulnar nerve at the elbow recording of sensory potentials at the wrist can be expected to show changes only if a proportion of the nerve fibres have undergone degeneration in their distal parts. It is believed that the sensory fibres contributing to the nerve action potential are the large myelinated fibres, so that the results obtained in pathological conditions provide no information about the small myelinated or unmyelinated fibres. The authors found it possible to equate electrical with clinical findings in these patients only in the most general terms, though they observed that all patients with sensory loss in the hand showed abnormalities in the test, whereas the converse was not true. It is concluded that as a diagnostic procedure the method provides objective information about the function of sensory nerve fibres without requiring any cooperation by the patient, except that he should lie still and relax. *R. Wyburn-Mason*

1411. **The Effect of Bemegride (" Megimide ") on Normal People**
J. H. MARGERISON. *Electroencephalography and Clinical Neurophysiology* [*Electroenceph. clin. Neurophysiol.*] **10**, 541–545, Aug., 1958. 4 figs., 12 refs.

The author, working at Runwell Hospital, Wickford, Essex, has studied the clinical and electroencephalographic (EEG) changes occurring in response to the intravenous injection of up to 150 mg. (30 ml. of a 5% solution) of bemegride in 10 healthy volunteers, of whom none had any personal or family history of fits or faints. In all the resting EEG was normal and no abnormality had appeared during overbreathing or photic stimulation. In order to remove subjective bias each subject was told that he or she would receive an injection of either distilled water or bemegride, though in fact all received bemegride.

Twitching of the eyelids occurred during the injection in 9 subjects and twitching of the peripheral musculature in 4; 3 subjects felt sick and 2 actually vomited, while dizziness was experienced by 7 and a sense of dissociation of some part or parts of the body by 6. In 8 cases there

were also subjective feelings of tenseness or of being unhappy or disturbed. Several subjects remarked that these sensations persisted for several hours, and 3 subjects observed that their tolerance for alcohol was considerably raised several hours after the injection. No actual clinical seizures occurred, but in 2 cases paroxysmal slow activity was seen in the EEG after 125 and 130 mg. of bemegride respectively and the injection was thereupon discontinued. In another case paroxysmal slow activity occurred during photic stimulation after the injection had been given. No focal abnormalities were observed. *John N. Walton*

1412. **Recurrent Multiple Cranial Nerve Palsies**
C. SYMONDS. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] **21**, 95–100, May, 1958. 5 refs.

The author describes in considerable detail the case histories of 4 patients, a man aged 22 and 3 women aged 27, 53, and 57 respectively at first onset, who suffered from a succession of cranial nerve palsies of rapid onset and transient duration, these occurring at irregular intervals over a period of several years. Apart from the possible involvement of a vestibular nerve in 2 cases, causing vertigo, only the motor nerves were affected. The 7th cranial nerve was involved in all cases, while in 3 cases cranial nerves on either side were affected. There was no evidence of involvement of the neuraxis. The cerebrospinal fluid was normal and the Wassermann reaction negative in all 4 patients.

The author suggests that these cases form a homogeneous group, the aetiology of which is of a toxic or infective character. The first case eventually proved to be due to a chronic tuberculous infection without pulmonary involvement. In the second there were symptoms suggestive of sarcoidosis. In the third case there was some, but not conclusive, evidence of tuberculous infection; the fourth patient later developed asthma. The author considers it possible that such recurrent palsies may represent a hypersensitivity reaction involving the connective-tissue elements of the cranial nerves or their meningeal coverings. *R. Wyburn-Mason*

1413. **Staphylococcal Spinal Meningitis**
T. C. STUDDERT. *British Medical Journal* [*Brit. med. J.*] **1**, 1457–1459, June 21, 1958. 18 refs.

Of 115 cases of pyogenic meningitis admitted to Cumberland Infirmary, Carlisle, between 1949 and 1956, 7 were due to staphylococcal infection. The evidence of meningitis was almost entirely referable to the spine, headache, mental clouding, disorientation, and convulsions being absent. The differential diagnosis from epidural abscess is discussed. *Staphylococcus aureus* was isolated in all 7 cases, the organism being fully sensitive to penicillin in 6 and partially sensitive in one. Generally, treatment consisted in a combination of intrathecal and intramuscular injections of penicillin with sulphonamides by mouth or intramuscularly. Of the 7 patients, 6 recovered completely; the remaining patient died within a few hours of admission to hospital. *Hugh Garland*

1414. **Progressive Multifocal Leuko-encephalopathy. A Hitherto Unrecognized Complication of Chronic Lymphatic Leukaemia and Hodgkin's Disease**
K.-E. ÅSTRÖM, E. L. MANCALL, and E. P. RICHARDSON. *Brain* [*Brain*] **81**, 93–111, 1958. 10 figs., 41 refs.

Three cases are presented of an unusual demyelinative disease process developing in adult life on a background of chronic lymphatic leukaemia (2 cases) and Hodgkin's disease (1 case). The lesions are characterized by widely disseminated small perivascular foci of destruction of myelin-sheaths with relative sparing of axis-cylinders. These foci have shown a pronounced tendency to become confluent so that large plaque-like lesions may occur. Most severely affected were the posterior parts of the cerebral hemispheres, although all levels of the brain could be involved. Associated with the myelin destruction was a distinctive cytological reaction consisting of hypertrophy of astrocytes into bizarre gigantic forms, with unequivocal mitoses in Case 1 suggesting neoplastic cells in appearance, and alteration of oligodendrocytes with the production of hitherto undescribed large round densely basophilic nuclei.

Review of the literature discloses 5 additional cases of the same neuropathological process occurring in a background of Hodgkin's disease in 2 cases, sarcoidosis in 1 case and tuberculosis in 1 case. In 1 case the underlying disease process, if any, is unknown. The clinical features of these cases are reviewed.

It is suggested that the neurological disease occurs as a complication of Hodgkin's disease or chronic lymphatic leukaemia, although its occurrence with other disease states implies that these diseases are not absolutely required for its production. The neurological disease cannot be related in any way to various forms of treatment used for Hodgkin's disease or chronic lymphatic leukaemia.

Evidence is adduced that we are dealing with a hitherto unrecognized neuropathological entity. The cause remains undisclosed.—[Authors' summary.]

BRAIN AND MENINGES

1415. **Intracranial Internal Carotid Artery Aneurysms. Results of Treatment by Cervical Carotid Artery Ligation**
H. A. SHENKIN, P. POLAKOFF, and B. E. FINNESON. *Journal of Neurosurgery* [*J. Neurosurg.*] **15**, 183–191, March, 1958. 11 refs.

The treatment of intracranial aneurysm of the internal carotid artery continues to be a subject of controversy, though most recent authorities appear to favour direct intracranial attack on the aneurysm. Nevertheless, the present authors report 19 consecutive cases treated by the other method, that is, proximal ligation of the carotid artery in the neck, which were followed up for periods ranging from 6 months to 7·5 (average 3·2) years, and present the results to support their view that this method of treatment is adequate for intracranial aneurysms on the internal carotid artery itself, since it carries a low mortality and morbidity rate while protecting against recurrent haemorrhage.

Of the 19 patients, 18 were first seen because of a spontaneous subarachnoid haemorrhage. All patients, except one who later died, were fully conscious at the time of ligation. In 8 cases the aneurysm was at the origin of the posterior communicating artery, in 5 at the bifurcation of the internal carotid artery, and in 5 between these two sites; thus all the aneurysms were below the circle of Willis. There was only one death, that of a man aged 59 who was semicomatose on admission, and only one patient developed permanent hemiplegia. The other 17 patients are well and can be regarded as "economically useful individuals". Temporary hemiplegia occurred in 5 cases after ligation, but cleared completely in 3 and in the other 2 improved sufficiently for the patient to work. In the authors' experience ligation of the internal carotid artery at an interval after ligation of the common carotid artery appeared to be the safest procedure. They found no evidence of higher morbidity among patients over 40 years of age, contrary to some previous reports by other workers. They issue the warning, however, that this form of treatment is not only ineffectual, but may actually be dangerous, when the aneurysm is situated on the anterior cerebral or anterior communicating artery.

J. V. Crawford

1416. **Primary Tumours of the Thalamus**
W. McKissock and K. W. E. Paine. *Brain* [*Brain*] **81**, 41–63, 1958. 9 figs., 21 refs.

The clinical picture of a group of 24 patients with tumours of the thalamus is outlined and an attempt made to explain the causation of symptoms. The pathological nature of the tumours, as far as information is available, is given. The characteristic ventriculographic appearances of thalamic tumours are described and illustrated. A rational method of palliative treatment by ventriculocisternostomy is advised. The results of such treatment are given and compared with other forms of therapy. Stress is laid upon the presence of a group of disturbances of ocular muscles, intrinsic or extrinsic, as a characteristic disturbance to be found in patients with tumours of the thalamus.—[Authors' summary.]

1417. **One Thousand Cases of Late Onset Epilepsy**
S. Sheehan. *Irish Journal of Medical Science* [*Irish J. med. Sci.*] 261–272, June, 1958. 6 refs.

A personal investigation is described of 1,000 cases of epilepsy in which the first attack of unconsciousness occurred at or after the age of 20 years. All the patients (632 male and 368 female) were seen in the Neurological Unit of the United Sheffield Hospitals and followed up for periods varying from 6 months to 10 years. Cerebral arteriography or air encephalography was carried out by the author in 950 of the cases. Care was taken to obtain a detailed history, with particular reference to the type of attack, whether focal or generalized, and the duration of the seizure.

In 552 (55%) of the cases a definite cause for the epilepsy was established as follows: primary cerebral tumour (106 cases); cerebral metastases (33); cerebral arteriosclerosis and hypertension (71); carotid thrombosis (15); middle cerebral artery thrombosis (3); migraine (109); angioma (14); minor vascular abnormalities (23); trauma (73); neurosyphilis (27); disseminated sclerosis (25); congenital lesions, including toxoplasmosis (6); chronic alcoholism (5); brain abscess (3); cysticercosis (2); pregnancy (9); and miscellaneous (28), including one case of hypoparathyroidism and one of insulin-secreting tumour of the pancreas. No specific aetiological factor was established in the remaining 440 cases, in 70% of which, however, the epilepsy was controlled by administration of various combinations of phenobarbitone, phenytoin, primidone, and a new glutonamide derivative. The author states that the patients in the latter group attend the neurological out-patient department and not a special clinic for epilepsy; she believes that under this arrangement the patients attend more readily. *G. S. Crockett*

1418. **The Narcolepsy Syndrome**
W. Ganado. *Neurology* [*Neurology (Minneap.)*] **8**, 487–496, June, 1958. 1 fig., bibliography.

This is a general account of the syndrome of narcolepsy based on the records of 128 patients, 60% of them males, treated for this disorder at the University of Michigan Hospital, Ann Arbor, in the course of 20 years. Associated phenomena occurred in a number of the patients, cataplexy being the commonest (54% of the cases), but fugue-like states, episodes of paralysis on relaxation or when going off to sleep (19%), reduced perceptual awareness, and hypnogogic hallucinations were also noted. In only one patient did the narcolepsy cease spontaneously, but in many others the attacks gradually became less frequent over the course of years, while the cataplectic attacks stopped completely in a number of patients. The author considers that the narcoleptic syndrome is a non-epileptic disturbance of subcortical origin; it appears to be a state of depression of the arousal system, due possibly to some neuro-humoral deficiency. *J. W. Aldren Turner*

1419. **Jacksonian Seizures in Infancy and Childhood**
J. Holowach, D. L. Thurston, and J. O'Leary. *Journal of Pediatrics* [*J. Pediat.*] **52**, 670–686, June, 1958. 1 fig., 11 refs.

Between 1934 and 1955 a total of 114 patients with Jacksonian or local motor epilepsy were seen at the Children's Hospital, St. Louis, Missouri. In half the cases seizures began before the age of 3 years, and in 27 out of 95 in which the family history was ascertained relatives suffered from epilepsy. Although Jacksonian epilepsy implies a local organic pathology, there was a definite cause for the convulsions in only 39 cases in the series—namely, birth injury (13), infantile hemiplegia (11), acquired disease of the central nervous system (12), telangiectasis (2), and probably febrile seizures (1). Contrary to the findings in adults, brain tumours are rare in children with Jacksonian epilepsy; the only patient in the present series who had a brain tumour had suffered a severe birth injury which may have been the cause of the fits rather than the neoplasm. Febrile seizures occurred before the onset of epilepsy in 6 of the

114 cases. Of the 87 patients without congenital or acquired hemiplegia, 40 had post-ictal paralysis, this being permanent without apparent cause in 16. Evidence of mental deficiency was present before the onset of seizures in 28 cases and in 4 others after recurrent convulsions.

Discussing the electroencephalogram, which was recorded in 83 cases, the authors suggest that a spike focus may well indicate only a discrete focus of high excitability within a much larger area of disturbed function and not necessarily a structural lesion. It may therefore be recorded on one occasion and not on another, in a different place, or on the opposite side in a later tracing. Slow-wave foci are likely to indicate an underlying lesion, particularly if they occur repeatedly at the same site.

Air encephalography was carried out only on selected patients, the criteria for this being increased intracranial pressure, the presence of neurological abnormalities, and failure to respond to adequate anticonvulsive therapy. *N. S. Alcock*

NEUROMUSCULAR DISEASES

1420. An Evaluation of Thymectomy in Myasthenia Gravis

J. A. SIMPSON. *Brain* [*Brain*] **81**, 112–114, 1958. 2 figs., 29 refs.

In this paper an attempt is made to assess the value of thymectomy in the treatment of myasthenia gravis by the analysis and follow-up study of 404 cases of the disease seen mainly at the National Hospital, Queen Square, but also at St. Bartholomew's and New End Hospitals, London, between 1934 and the time of writing, the results being compared with those of other workers, particularly in the U.S.A.

It is concluded that there is a substantial chance of improvement after thymectomy in all cases, and that this is most evident if the duration of the illness is less than 5 years and there is no evidence of a thymoma. In cases operated on more than 7 years after the onset improvement is less likely, but the risk of death from myasthenia has by this time already become smaller. Improvement occurs in both sexes, but its extent is more significant in women. In the presence of a thymoma the prognosis for life is poor and only one patient in 3 survives, but in the survivors the myasthenia may improve following operation as much as in those without tumour. Maximum improvement occurs in patients in whom the symptoms first appeared at an early age. Death from myasthenia is more probable in those requiring large doses of neostigmine.

[Anyone proposing to assess the value of any form of treatment of myasthenia gravis is advised to read this paper, though he will find it very hard going. It is unfortunate that the author does not discuss the experience of this disease at Leeds reported by Garland and Clark (*Brit. med. J.*, 1956, **1**, 1259; *Abstr. Wld Med.*, 1956, **20**, 475), since it is very similar to that reported from Manchester by Ferguson *et al.* (*Lancet*, 1955, **2**, 636; *Abstr. Wld Med.*, 1956, **19**, 234), which he reviews, and also covers roughly the same period as that of the Manchester series and the present study.]

Hugh Garland

1421. Use of Oximes in the Treatment of Intoxication by Anticholinesterase Compounds in Patients with Myasthenia Gravis

D. GROB and R. J. JOHNS. *American Journal of Medicine* [*Amer. J. Med.*] **24**, 512–518, April, 1958. 4 figs., 14 refs.

Administration of pyridine-2-aldoxime methiodide (2-PAM) or diacetyl monoxime (DAM) to patients with myasthenia gravis reversed the effects of the following anticholinesterase compounds on neuromuscular function, muscle strength, and plasma and red blood cell cholinesterase activity: neostigmine, bis-neostigmine, pyridostigmine, bis-pyridostigmine, ambenonium, and "sarin". The intravenous dose of these oximes that reversed the effect of anticholinesterase agents on general strength was 300 to 2,000 mg. Following the administration of sufficient anticholinesterase compound to repair the myasthenic defect in neuromuscular transmission and improve strength, the injection of oxime resulted in a decrease in transmission and strength, toward the basal level. Following an excess of anticholinesterase agent sufficient to cause neuromuscular block and weakness the injection of oxime resulted in improvement in neuromuscular function and strength. The subsequent injection of oxime resulted in some instances in a decrease in function and strength to the basal level.

The oximes have proved to be of value in the management in myasthenic patients of weakness due to overtreatment with anticholinesterase medication.—[Authors' summary.]

1422. Relationship of Dystrophia Myotonica (Myotonic Dystrophy) and Myotonia Congenita (Thomsen's Disease)

J. E. CAUGHEY. *Neurology* [*Neurology* (*Minneap.*)] **8**, 469–476, June, 1958. 4 figs., 26 refs.

From Otago Medical School, New Zealand, comes this study of a family in which the older members suffer from dystrophia myotonica, whereas one member of the second generation presents a picture of myotonia congenita (Thomsen's disease). Brief histories are given of 2 brothers in the first generation who suffered from both dystrophia myotonica and Paget's disease of bone. The son of one of these men had noticed difficulty in relaxing his grip all his life and at the age of 9 had noticed stiffness of the muscles. At the age of 35 he was found to have myotonia of the grip (which passed off after gripping three times), hypertrophy of the masseter, biceps, and forearm muscles, pseudo-hypertrophy of the thigh and calf muscles, and mechanical myotonia of the calves. There was no muscle atrophy and, apart from frontal baldness, no other dystrophic signs. The author suggests that this family presents an intermediate form between the two recognized forms of myotonic dystrophy, and that observation of similar families might well explain the divergence of opinion on the relationship between dystrophia myotonica and myotonia congenita.

J. W. Aldren Turner

Psychiatry

1423. **The Cure of Homosexuality**
J. A. HADFIELD. *British Medical Journal* [*Brit. med. J.*] **1**, 1323–1326, June 7, 1958.

The author emphasizes that homosexuality can be cured by psychotherapy if it is possible to trace it back to its basic cause in infantile experience, though treatment is usually so difficult and time-consuming, and is so often unsuccessful, that he himself no longer accepts homosexuals for treatment. He mentions, however, 4 patients whom he treated over 30 years ago and cured completely, in that they lost their propensity for their own sex and became interested in the opposite sex instead. Two of these had married and had children, but preferred homosexual relationships, while the other 2 were non-practising homosexuals with an attraction to boys' buttocks, which were to them substitutes for the breast. Four more recent cases which were treated and cured are also described briefly. Two of the patients were young practising homosexuals; one responded to only 5 treatment sessions, whereas the other needed 164 sessions. The other 2 were non-practising homosexuals who were cured after prolonged therapy. *F. K. Taylor*

1424. **Clinical Trial of Acepromazine Maleate in Chronic Schizophrenia**
J. F. COLLARD and R. MAGGS. *British Medical Journal* [*Brit. med. J.*] **1**, 1452–1454, June 21, 1958. 7 refs.

A trial of the phenothiazine derivative acepromazine maleate ("notensil") in the treatment of chronic schizophrenia was carried out at Hellingly Hospital, Hailsham, Sussex. The patients taking part, who were divided into (A) a treatment group of 38, and (B) a control group of 40, were drawn from among those relapsing after the withdrawal of chlorpromazine; they were chosen from various wards and allocated to the two groups in random order. During the 6 weeks' treatment period weekly ratings were made of the clinical condition by the physician, using Boardman's scale, and of behaviour by the nursing staff, using the scale of Baker and Thorpe. A final clinical assessment of the efficacy of treatment was made by classification of the patients into three groups—improved, not improved, and worse—while separate statistical assessments were made of the changes in the two ratings. The drug was given orally in tablet form in doses of 50 mg. 3 times a day initially, increasing by 50 mg. a day to 100 mg. 3 times a day by the 4th day. Patients in Group B received placebo tablets.

The distribution of clinical types was much the same in the two groups. Both contained approximately equal numbers of males and females, the average age was 48 in Group A and 44 in Group B, and the average duration of stay in hospital in each was 13 years. Among other forms of treatment, 25 patients in each group had received electric convulsion therapy, 4 in Group A and 8 in Group B had undergone leucotomy, and 4 and 20 respectively had received tranquillizers. Parkinsonism, jaundice, and dermatitis were not observed as side-effects, but there was a high incidence of hypotensive reactions to the drug, which necessitated the withdrawal from the study of 4 of the 42 patients originally in Group A. Even a dose of 10 mg. caused a considerable fall in blood pressure. In one case this was associated with drowsiness and depression of the corneal and limb reflexes, followed by a major epileptic fit, and it is suggested that acepromazine, like promazine and chlorpromazine, is able to potentiate epilepsy.

There were no significant changes in the behaviour ratings and although the clinical ratings showed some improvement, this did not reach a high level of significance. On the other hand the final clinical assessments showed a highly significant difference between the groups, 9 patients in Group A being improved and only one in Group B. In discussing the validity of their findings the authors mention some of the problems arising in the organization of therapeutic trials, such as the need for a "good" placebo and the liability of the nursing staff to regard the double-blind method as a challenge to them to find out which patients are receiving the active drug and which the placebo. *John C. Kenna*

1425. **Treatment of the Acute Complications of Chronic Alcoholism. Use of Azacyclonol ("Frenquel") Hydrochloride in One Hundred Consecutive Cases**
J. C. TRAVIS. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **167**, 156–159, May 10, 1958. 8 refs.

Azacyclonol hydrochloride ("frenquel") was tried in the treatment of the acute complications of chronic alcoholism in 100 consecutive patients attending the Adult Guidance Center, Department of Public Health, San Francisco. The average age of the patients was 42·4 years (range 27 to 66 years) and their occupations varied widely. Symptoms ranged from hallucinations to marked confusional states and delirium tremens. The duration of the drinking bout varied from one day to 8 months; only 12 patients had abstained for more than a few days before seeking treatment. Analysis of the incidence of organic and psychiatric disorders showed that peripheral neuritis was the most common. The average dose of azacyclonol was 100 mg. 4 times a day; it was usually given by mouth, but in a few cases intravenous administration was necessary to allay symptoms. In all cases the drug was an adjuvant to the usual treatment given in severe cases.

The results were encouraging, 84 of the patients being considered recovered or improved. There was immediate relief of symptoms following intravenous injection and a more gradual response after oral administration. Several cases are described. *J. MacD. Holmes*

Dermatology

1426. The *p*H of the Skin Surface of Children with Seborrhoeic Dermatitis Compared with Unaffected Children

J. M. Beare, E. A. Cheeseman, A. A. H. Gailey, and D. W. Neill. *British Journal of Dermatology* [*Brit. J. Derm.*] **70**, 233–241, July, 1958. 1 fig., 9 refs.

The *p*H of the skin surface of 45 young children with seborrhoeic dermatitis and 45 controls matched for age and sex was studied at the Royal Victoria Hospital, Belfast, the *p*H being determined at 16 different body sites by the glass-electrode technique. The mean *p*H at affected sites in seborrhoeic children was higher than would have been expected from the corresponding control observations. The unaffected sites in the seborrhoeic group showed a similar trend towards a more alkaline skin surface than the normal children, although the differences were less marked than for the affected areas of the body.

It is concluded that in general seborrhoeic patients have a more alkaline skin surface, suggesting an underlying constitutional disturbance rather than an infective condition peculiar to the skin. The fact that the skin of the patient with seborrhoea is alkaline may indeed be a reason for the frequent surface infections.

G. W. Csonka

1427. Comparison of the Antipruritic Effect of Morphine and Papaverine in Experimental and Pathological Itch in Man

S. G. Macris, G. M. Smith, and H. K. Beecher. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol. exp. Ther.*] **123**, 220–223, July, 1958. 2 figs., 16 refs.

The effect of papaverine, morphine, pentobarbital, aminophylline, tripelenuamine, and placebo was tested on experimental pruritus induced with cowhage. Only papaverine reduced experimental pruritus to a statistically significant degree. Since papaverine has been shown in another study in this laboratory [Harvard Medical School, Boston] not to have analgesic power greater than that associated with placebos, this raises some question about the theory that the same apparatus mediates itch and pain.—[Authors' summary.]

1428. Studies in Contact Dermatitis. I. General Principles in Patch Testing

D. C. G. Bett and C. D. Calnan. *Transactions of the St. John's Hospital Dermatological Society* [*Trans. St John's Hosp. derm. Soc.* (*Lond.*)] No. 39, 20–27, 1957 [received June, 1958]. 20 refs.

Writing from St. John's Hospital for Diseases of the Skin, London, the authors state that patch tests are frequently misused in the clinical assessment of contact dermatitis, subject as they easily are to misinterpretation. They point out that the patch test is designed to be a specific test for antibodies of the delayed type of allergy. The finding of a positive reaction to the test does not necessarily link the allergen to the dermatitis under study, unless the clinical facts support the theory.

In the interpretation of a positive reaction a decision must be made as to whether the reaction is an irritant or an allergic response. Attention is drawn to the following points: (1) the nature of the material; thus detergents are frequently irritant, while cosmetics rarely are so; (2) successive dilutions, to 10% or less, of a sensitizing material will give a graduated response, whereas dilution of an irritant may give a negative response even at a concentration as high as 50%; (3) the use of control subjects and repetition of the test is also helpful.

Some of the causes of false positive results are: the patient may be in status eczematicus, the test area may be adjacent to a previous strong reaction, or an organic or other unsuitable carrier may have been used for the test substance. False negative reactions may be encountered when there is either inadequate concentration of the material (several dilutions should be used) or inadequate penetration of the skin, especially when solid materials are being tested. Regarding the actual technique of the test, the authors point out that the usual dilution tables used (those of Sulzberger and Rostenberg), useful as they are, often give too strong a concentration of the test material and a very severe reaction may result. This is a further argument for the use of several dilutions. Finally the reading of the test should be made not only at 48 hours when the patch is removed, but also at 96 hours, in order to include any delayed responses, which, in the authors' experience, occur in some 10% of cases.

Allene Scott

1429. Studies in Contact Dermatitis. II. Lipstick Cheilitis

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Cheilitis due to lipstick has accounted for nearly half the patients with cosmetic contact dermatitis seen at St. John's Hospital for Diseases of the Skin, London, during the past 4½ years. Included in the composition of the lipstick are: (1) the base, which very occasionally gives rise to reactions; (2) a perfume, also rarely the source of trouble; and (3) the colouring substance (a combination of eosin, various "lakes", and azo dyes). The eosin appears to be the major allergenic factor, most commonly as a direct factor, but occasionally only after exposure of the patient to light.

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The typical clinical picture of a dry scaling dermatitis at the sites of contact of the lip with the stick can be fairly easily differentiated from that seen in other disorders by reason of its strict localization and the usual absence of angular involvement. The reaction may

appear within a few hours of using the lipstick or may develop only after several years' use; the allergy, once developed, is permanent. Recovery after abandoning use of the offending lipstick may not be complete for several weeks.

At this point a patch test should be carried out, using the patient's lipstick, eosin, and a non-eosin containing lipstick. Eosin should be used in concentrations up to 50%, since about 10% of lipsticks will be found to react only at this level. If reaction occurs to the first two constituents named, but not to the non-eosin lipstick, then the latter can be used by the patient without ill effect except in the case of a positive reaction to eosin in a concentration of 50%, when it has been found that neither an eosin or other indelible stick can be used.

Allene Scott

1430. **Histopathology of Contact Eczema with Reference to Sweat Retention**

D. I. McCALLUM. *Transactions of the St. John's Hospital Dermatological Society* [*Trans. St. John's Hosp. derm. Soc. (Lond.)*] No. 39, 5–8, 1957 [received June, 1958]. 10 figs., 11 refs.

In this study, reported from the Nottingham and Newark Hospitals Group, an attempt was made, by means of serial histological examination of some 9,000 sections of skin biopsy specimens, to follow the development of the true eczematous reaction as produced by a positive patch test. Three observations are of importance. (1) Within 6 hours, before any visible change has occurred and while the epidermal reaction is still minimal, the dermal reaction is well developed, particularly around sweat-duct orifices and pilo-sebaceous glands, ostensibly the portals of entry for the allergen. (2) The primary degeneration appears to start in the rete mucosum surrounding the sweat ducts, producing a vertical column of deteriorating rete cells which are unable to withstand the increasing pressure of the capillary infiltrate in the dermis, thereby permitting the development of the vesicle. (3) Finally, the sweat ducts traversing the involved area appear to be able to withstand the increased pressure of the vesicle which, however, may rupture into the stratum corneum around the ampulla of the duct, the duct itself remaining intact. On the other hand, if no vesicular rupture occurs, then the duct may give way and empty into the vesicle itself. This last finding may, it is suggested, explain the sweat retention seen in some cases of eczema.

Allene Scott

1431. **Histopathology of Patch Tests**

D. I. McCALLUM. *Transactions of the St. John's Hospital Dermatological Society* [*Trans. St John's Hosp. derm. Soc. (Lond.)*] No. 39, 11–19, 1957 [received June, 1958]. 17 figs., 10 refs.

On the basis of the author's histopathological study [see Abstract 1430] of the development of the eczematous allergic patch-test reaction the possible steps in the pathogenesis of eczema are here discussed. Entry of the allergen appears to be via the sweat and pilo-sebaceous structures. The earliest visible reaction takes place within 6 hours in the dermis, around the proximal end of the sweat duct. By the end of 12 hours there is degeneration of the epidermal cells adjacent to the duct, while between 12 and 24 hours the capillary infiltrate increases rapidly, exerting considerable pressure on the area of epidermal degeneration. The vesicle forms as a result of the rapid penetration of fluid through the broken epidermal barrier, compressing adjacent cells as well as the sweat duct. If rupture of the latter occurs at all, it occurs near the ampulla in the lower stratum corneum. When vesiculation is complete the cells of the rete mucosum, in a reparative attempt, seal or at least partially seal the breach, and the fluid is reabsorbed.

The author points out that this concept of the participation of the sweat duct in the process is contrary to the view generally held that eczema is an allergic process in which the epidermis is the "shock" tissue and the changes in the upper dermis are merely secondary, both in development and in importance. *Allene Scott*

1432. **Clinical and Pathologic Findings in the Skin in Anaphylactoid Purpura (Allergic Angiitis)**

R. K. WINKELMANN. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] 33, 277–288, May 28, 1958. 5 figs., 12 refs.

Acute episodes of non-thrombocytopenic purpura secondary to inflammation of the walls of small dermal blood vessels have been variously termed purpura rheumatica, Schönlein–Henoch syndrome, anaphylactoid purpura, allergic angiitis, allergic vasculitis, Gougerot's nodular allergid, erythema elevatum diutinum, and polyarteritis nodosa (superficial type). Other related syndromes are systemic angiitis, lethal granuloma of the nasopharynx, allergic granulomatosis, Wegener's granulomatosis, temporal arteritis, and polyarteritis nodosa (systemic). Some of the relationships between various forms of the reaction in the cutaneous and systemic vasculature are described. There may be sensitivity to therapeutic agents or to such chemicals as weed-killers and insecticides; the condition has followed the injection of serum or other proteins. The onset is acute and may be marked by fever, arthralgia, headache, and mild gastro-intestinal disturbance. Haemorrhage occurs in the skin as in other tissues. The cutaneous manifestations are symmetrical and may be localized to dependent parts of the body.

The histological findings are described, particularly acute necrosis of the vessel walls, which, the author states, is diagnostic. *S. T. Anning*

1433. **The Treatment of Psoriasis and Other Dermatoses with Triamcinolone (Aristocort)**

W. B. SHELLEY, J. S. HARUN, and D. M. PILLSBURY. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **167**, 959–964, June 21, 1958. 3 figs., 5 refs.

The authors present, from the University of Pennsylvania Medical School, Philadelphia, a short-term review of the effects of triamcinolone, a recently introduced fluoroprednisolone steroid, in the treatment of 60 patients with psoriasis and 70 with other dermatoses. The cases were unselected, all forms and degrees of psoriasis were included, and only rapid and unquestion-

able therapeutic effects were accepted in the assessment. The dosage of triamcinolone varied from 4 to 32 mg. orally per day, the usual dose being 4 mg. four times daily; low rather than high dosage was preferred, but the maintenance level was not usually below 8 mg. per day. Gradual tapering-off of the dosage was regarded as being as important as with the other steroids. In most cases local treatment was suspended.

There was a prompt temporary clearing effect in as many as 37 (60%) of the cases of psoriasis, the scaling and erythema diminishing significantly within one week. With continued adequate dosage the psoriasis in some patients completely disappeared in 2 to 4 weeks; however, upon cessation of treatment or reduction of the dose the lesions regularly returned, sometimes in more aggravated form. The remaining 23 cases of psoriasis (40%) failed to respond for no apparent reason, but it is noted that in 9 out of 21 of these patients there was also no local response to a skin test with a 1% triamcinolone suspension, whereas in all the other 12 patients who responded to triamcinolone orally the skin tests showed a sharply circumscribed area of complete involution at the site of the triamcinolone injection. The authors' early impression is " that an eczematoid histological cast to the psoriasis patterning is correlated with triamcinolone responsiveness "; and therefore skin biopsy findings may possibly be of prognostic value. They recommend reserving the use of triamcinolone for acute extending psoriasis not controllable by other means or for cases of very severe chronic psoriasis. Topical application of triamcinolone in ointment was without effect on the psoriasis, possibly because adequate amounts cannot be absorbed.

The other dermatoses treated included chronic eczematous eruptions, localized neurodermatitis, contact dermatitis, seborrhoeic dermatitis, and alopecia areata. It appeared that 4 mg. of triamcinolone was often equivalent to as much as 10 mg. of prednisolone in the treatment of inflammatory dermatoses. Triamcinolone was helpful in alopecia areata and seemed to have a greater stimulant effect on hair-growth than the other steroids. The side-effects otherwise were similar to those produced by any corticosteroid, except for the unusual effect of intense generalized flushing and hyperhidrosis observed in 2 patients 30 to 45 minutes after taking a tablet of triamcinolone. *E. W. Prosser Thomas*

1434. **Nephritic Melanodermia. Report of Two New Cases.** (La mélanodermie brightique. (À propos de deux nouvelles observations))
H. Thiers, P. P. Ravault, D. Colomb, and E. Lejeune. *Annales de dermatologie et de syphiligraphie* [*Ann. Derm. Syph. (Paris)*] **85**, 267–277, May–June, 1958. 8 figs., 4 refs.

That melanodermia can be a complication of Bright's disease has been known for 30 years, but as the authors (writing from the Skin Clinic of the Hôpital Édouard-Herriot, Lyons) point out, it is very rarely reported. They therefore describe 2 further cases. Their first patient was a woman aged 60 with chronic nephritis who at the age of 37 had had acute nephritis with albuminuria and oedema, but apparently no increase in her blood pressure. On admission to hospital in 1956 she had albuminuria, a blood urea level of 150 mg. per 100 ml., and a blood pressure of 240/130 mm. Hg. There was widespread hyperpigmentation, most marked on the exposed parts, but not affecting the mucous membranes. Skin biopsy examination revealed a thin epidermis with absent granular layer and a flat epidermo-dermal junction. Throughout the epidermis there was a large amount of melanin, but none was found in the corium.

The second patient was a woman aged 52 suffering from chronic nephritis and severe hypertension. When the blood urea level rose above 400 ml. per 100 ml. pigmentation appeared. The distribution of the pigmentation and the histological findings in the skin were as in the first patient, except that melanin was found lying free and in small macrophages in the corium. The authors state that in this condition the brown coloration is homogenous and always spares the mucous membranes, genitalia, and nipples. *E. Lipman Cohen*

1435. **Treatment of Partial and Total Alopecia with ACTH and Cortin.** (Лечение больных гнездной и тотальной плешивостью АКТГ и кортином)
G. Ja. Šarapova and M. D. Bagnova. *Проблемы Эндокринологии и Гормонотерапии* [*Probl. Endokr. Gormonoter.*] **4**, 111–112, No. 2, March–April, 1958. 14 refs.

In alopecia there is a disturbance of the neuro-endocrine balance, and the majority of patients with partial and all those with total alopecia show a diminution in the urinary 17-ketosteroid content. Various authors have shown that ACTH (corticotrophin) and " cortin " [an adrenal cortical extract] are effective in correcting this, and in some cases lead to renewed growth of the hair.

The present authors describe 20 patients (6 men and 14 women) who were treated on these lines, of whom 11 had partial alopecia, 5 total alopecia, and 4 seborrhoeic baldness. All were neurotic, with easy fatigability and emotional instability, and in 15 there was evidence of endocrine disturbance, for example, gonadal hypofunction with infantilism and sterility. All the patients with total alopecia were women, of whom 3 suffered from infantilism and sterility and 2 had premature onset of the menopause. ACTH was administered intramuscularly (15 to 20 units daily to a total dosage of 600 to 700 units), while cortin was given subcutaneously in doses of 10 units 3 times a week to a total of 20 to 40 injections. Clinical cure was achieved in 8 cases (5 of partial and 3 of total alopecia), while 6 others as well as 2 of seborrhoeic baldness were improved; 2 cases of total alopecia and 2 of seborrhoea showed no improvement. In the 16 patients who responded to treatment the urinary 17-ketosteroid excretion increased 3- to 4-fold and remained normal after treatment. The 3 cases of alopecia totalis which improved and the 4 resistant cases showed only insignificant and transitory increases in the urinary excretion of 17-ketosteroids. Relapse occurred in 2 of the cured cases in the course of a year, but a further course of treatment again produced a beneficial effect. *L. Firman-Edwards*

Paediatrics

NEONATAL DISORDERS AND PREMATURITY

1436. **Perinatal Pulmonary Pathology**
J. N. Briggs and G. Hogg. *Pediatrics* [*Pediatrics*] **22**, 41–48, July, 1958. 4 figs., 9 refs.

The pulmonary changes in 110 live-born and 26 stillborn infants seen at the General Hospital, Winnipeg, between September, 1954, and February, 1957, are described, and the natural history of lung changes in these infants is discussed. Pulmonary factors were the chief cause of death in 68 of the live-born infants and a contributory cause in the remaining 42. Microscopical examination of lung sections revealed seven pathological categories—stillborn lung, immature lung, atelectasis, collapse with hyaline membrane, collapse without hyaline membrane but of hyaline type, pulmonary haemorrhage, and pneumonia—the most frequent being hyaline membrane or collapse of the hyaline type (46 cases), pneumonia (27 cases), and atelectasis (16 cases). The peak incidence of collapse of the hyaline type occurred within 12 hours of birth and of hyaline membrane 12 to 24 hours after birth. The incidence of pneumonia showed two peaks—namely, within 12 hours of birth and after 48 hours.

From a review of their pathological material the authors conclude that collapse of the hyaline type precedes the formation of true hyaline membrane and may be followed by intrapulmonary haemorrhage. *R. M. Todd*

1437. **Prolonged Obstructive Jaundice in Infancy. V. The Genetic Components in Neonatal Hepatitis**
D. Yi-Yung Hsia, J. D. Boggs, S. G. Driscoll, and S. S. Gellis. *A.M.A. Journal of Diseases of Children* [*A.M.A. J. Dis. Child.*] **95**, 485–491, May, 1958. 20 refs.

In a previous study of prolonged neonatal jaundice not associated with erythroblastosis foetalis or biliary atresia (Gellis *et al.*, *A.M.A. J. Dis. Child.*, 1954, **88**, 285; *Abstr. Wld Med.*, 1955, **17**, 233) the authors reported a series of cases of the condition known variously as neonatal or infantile hepatitis, "giant-cell" hepatitis, or inspissated bile syndrome of unknown aetiology. In this condition jaundice appears during the first weeks of life, with acholic stools, bile in the urine, and moderate enlargement of the liver and spleen. The serum bilirubin level is increased, and histological examination shows degeneration of the liver cells with formation of multinucleate "giant cells". Full recovery occurs in 60% of cases; of the remainder some develop cirrhosis and a few die, usually from liver failure or from the complications of surgery.

The possibility of a genetic aetiology is now suggested as a result of a study of 59 families with one or more affected infants, 47 of the index cases being those previously reported from the Children's Medical Center, Boston, to which have been added 9 from the files of the Children's Memorial Hospital, Chicago, and 3 others from the literature. The 59 propositi had 61 siblings, of whom 11 developed the disease, whereas in a control series of 33 cases of proved bile-duct atresia none of the 40 siblings had jaundice in infancy. A very low incidence of a history of jaundice in either parent was found, suggesting that neonatal hepatitis is not transmitted as a Mendelian dominant. On the other hand the proportion of affected offspring closely approaches the figure computed by Weinberg's sib method, so that the data are consistent with a recessive mode of inheritance. There was no significant difference in incidence between the sexes. There was no instance of consanguinity, and in no family was there a known history of neonatal hepatitis in relatives other than the siblings. Of the only twins in the series, both were affected (it was not known whether they were mono- or dizygotic); the affected child was the only one in 21 families and the last child in 24; and in the remaining 13 familes the distribution of affected children was random, normal children being born before and after affected children and all 3 children in one family being affected. Complete recovery occurred in 41 and sequelae or death in 27 of the cases in which the outcome was known; the prognosis did not appear to be worse in families in which more than one child was affected.

The authors find that there is insufficient evidence to support the theory that neonatal hepatitis is due to any known virus (such as the inclusion-cell virus or the viruses of infective and homologous serum hepatitis) and consider that they have at least established the need to take seriously the possibility of a genetic aetiology.
A. White Franklin

1438. **Neonatal Tetanus in Nigeria**
A. B. Tompkins. *British Medical Journal* [*Brit. med. J.*] **1**, 1382–1385, June 14, 1958. 16 refs.

In this series of 141 cases of tetanus in newborn infants, reported from University College, Ibadan, Nigeria, the mortality was 89·6% and the incidence was highest during the dry season, doubtless owing to the greater amount of dust then present. The infection presumably occurred during the treatment of the umbilical cord at birth, and it may be assumed that the infant's age at onset represents the incubation period, which for the 14 patients (out of 135) who recovered averaged 10·7 days, compared with 7·3 days for the 121 fatal cases. The "onset interval", defined as the period between the appearance of the first symptom and the onset of the tetanic spasms, was significantly longer in the non-fatal than in the fatal cases. Division of the cases into two broad groups according to severity showed that the mortality was greater (97·8%) in the severe group, but nevertheless was very high (72·7%) even in the cases

assessed as mild or moderate. In the 102 patients in whom the temperature never fell below 98° F. (36·7° C.) the mortality was higher (100%) than in the remaining 33 (86·3%).

The clinical picture, which is described, presented no unusual features. Failure to suck from the breast was always the initial symptom. Tetanus antitoxin was given to all patients, 50,000 units being considered the optimum dose. The details of sedation and feeding of these babies are described. The author stresses the importance of the respiratory complications.

Winston Turner

1439. **Case for Induction of Labour in Treatment of Haemolytic Disease of the Newborn**

G. A. KELSALL, G. H. VOS, and R. L. KIRK. *British Medical Journal* [*Brit. med. J.*] **2**, 468–473, Aug. 23, 1958. 22 refs.

In this paper from King Edward Memorial Hospital, Subiaco, Western Australia, the place of induction of labour in the management of haemolytic disease of the newborn is discussed. It is stated that serial estimations of the antibody titre of maternal serum, as determined by a carefully standardized indirect antiglobulin technique, provide a reliable method of forecasting the severity of the disease in the infant. It will also indicate whether premature induction of labour is necessary and when exchange transfusion is required. The antibody titre of the serum of all Rh-negative pregnant women should be determined regularly at weekly or fortnightly intervals beginning at the 26th week of pregnancy. If the titre is 1 in 64 or less the infant will not require any treatment, but if the titre is higher than 1 in 128 the infant will need prompt exchange transfusion. Labour should be induced at the 35th week if the titre is 1 in 512 or higher, and at 37 or 38 weeks if the titre is 1 in 128 or 1 in 256. The longer the titre has been at 1 in 512 or higher, the more urgent is the need for both induction of labour and prompt exchange transfusion. The authors have calculated a "titre index" which they find helpful in estimating the increase in severity of the disease which "will occur if pregnancy is allowed to continue for any particular length of time". They conclude that early induction of labour in all cases in which the antiglobulin titre of the maternal serum indicates the need, followed by prompt and adequate exchange transfusion, would reduce the over-all foetal mortality by 11%—or in other words, one out of every 3 foetal deaths would be prevented.

Winston Turner

1440. **Meat in the Diet of Premature Infants. II. Influence on Red Cell Volume and Hemoglobin Mass**

T. R. C. SISSON and L. E. WHALEN. *A.M.A. Journal of Diseases of Children* [*A.M.A. J. Dis. Child.*] **95**, 626–636, June, 1958. 4 figs., 14 refs.

The investigation herein reported from the University of Rochester School of Medicine, New York, was undertaken to determine whether meat would be an effective source of iron in the diet of premature infants. Of 44 premature infants in good condition weighing from 1,300 g. to 2,300 g., 15 received a meat supplement to the diet and 29 served as controls. The test infants, starting at 2 to 4 weeks of age, were at first given 10 g. of meat with the daily diet, the meat supplement being increased to 75 to 100 g. at the age of 6 weeks. The findings for each infant are tabulated by age at the time of the test and by group. After the initial decrease in haemoglobin concentration, haemoglobin mass, haematocrit value, and erythrocyte volume which is observed in all premature infants there was a temporary increase in all these values in the meat-fed infants between 6 and 8 weeks of age. This increase was not observed in the controls until the 12th week. A steady decline in these values during the first year to low levels was noted in the control group, necessitating iron therapy in some instances. The serum iron concentration decreased throughout the period of study in the control subjects but in the meat-fed group levelled off until the 30th week and then increased.

It is concluded that meat provides an excellent source of protein for the infant and is an acceptable and utilizable source of iron in natural form.

J. M. Smellie

1441. **ABO Incompatibility and Haemolytic Disease of the Newborn**

G. H. VALENTINE. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **33**, 185–190, June, 1958. 10 refs.

The author reports from the Elgin General Hospital, St. Thomas, Ontario, that in a consecutive series of 1,000 live births clinically detectable jaundice appeared during the first 24 hours of life in 21 babies. The jaundice was due to Rh incompatibility in 7 cases, which are therefore excluded, the remaining 14 forming the subject of this study. The initial serum bilirubin levels varied between 4·0 and 13·0 mg. per 100 ml. [showing that lesser degrees of jaundice are very difficult to detect clinically], while in 3 full-term babies the maximum bilirubin level reached 20 to 25 mg. per 100 ml.; these 3 were treated by exchange transfusion.

None of the infants were anaemic; spherocytosis was observed in 8 cases and an excess of reticulocytes in 3. Serial tests showed that haemolysis first appeared in sodium chloride concentrations ranging from 0·52 to 0·84%. The direct antiglobulin test of Coombs gave a positive result in only one case. The blood of all 14 mothers of these infants was of Group O, whereas that of 12 of the infants was of Group A and of 2 of Group B, so that there was ABO incompatibility in all pairs; 7 babies were Rh-negative. In 11 cases maternal antibodies 2 to 4 days after the birth showed high titres against the factor carried by the baby, though it was not always a fully consistent finding. All 14 infants were considered to be suffering from ABO haemolytic disease. The haematological and serological findings showed no significant difference between severely and mildly jaundiced infants, thus providing no means of forecasting which baby would eventually require treatment. It is estimated that ABO haemolytic disease can occur in clinically recognizable forms in 7% of AB-incompatible mother–child pairs.

John Lorber

1442. **Hydramnios as a Signal to the Physician Responsible for Newborn Infants**

V. R. DE YOUNG. *Journal of Pediatrics* [*J. Pediat.*] **53**, 277–284, Sept., 1958. 1 fig., 10 refs.

CLINICAL PAEDIATRICS

1443. **Chronic Asthma in Childhood: Double-blind Controlled Study of Treatment with Gamma-globulin**
R. S. Abernathy, E. L. Strem, and R. A. Good. *Pediatrics* [*Pediatrics*] **21**, 980–993, June, 1958. 30 refs.

To evaluate the effect of injections of gamma-globulin upon the course of asthma, observations were made with 22 asthmatic children ranging in age from 1½ to 15½ years. They had suffered from asthma from one to 13 years and were selected as subjects because they had not made satisfactory improvement under allergic management over an average of 2·4 years. They were placed in two groups by random assignment, one of which received injections of gamma-globulin.

Without knowledge of the treatment being given, one author examined each child at the time of each injection and one month after the last injection. Roentgenograms, vital capacity, complete blood counts and chemical determination of the blood proteins were performed at the initial and final visits. Fifteen of the 22 patients improved clinically, 8 in the treatment group and 7 in the control group. No significant differences between the groups were noted in the amount of asthma, physical growth, hemoglobin value or eosinophilia. The concentration of gamma-globulin in the serum increased in the treated patients. Nevertheless, there was no difference in the incidence of infection in the two groups and in both it was equal to that in a normal population.

This double-blind controlled study offers no evidence to support the view that treatment with gamma-globulin has a beneficial effect on the course of chronic asthma in children.—[Authors' summary.]

1444. **Enteritis Due to *Escherichia coli* in Infants.** (О коли-энтерите у детей грудного возраста)
I. V. Cimbler, T. S. Sokolova, and T. A. Homickaja. *Педиатрия* [*Pediatrija*] **36**, 3–9, No. 5, May, 1958. 4 figs., 27 refs.

Diarrhoea and dyspepsia in infants are often due to infection with pathogenic strains of *Escherichia coli*, especially Types O111B4, O55B6, and O25B5 (Kauffman). The first of these types (corresponding to Type A4 of Adam) produces the severest toxic symptoms, particularly in infants in the first 6 months of life; in patients over the age of one year the organisms may be retained, the child becoming a carrier and thus a danger to younger infants. Enteritis due to *Esch. coli* is contagious and may give rise to widespread epidemics.

Out of 204 infants with enteritis studied at the Institute of Paediatrics, Moscow, the stools of 99 (48·5%) were found to contain pathogenic strains of *Esch. coli*; of these patients, 55 were under 6 months of age. *Esch. coli* Type O111B4 was isolated in 66 cases, Type O26 in 20, and Type O55 in 13. Necropsy on the 3 children who died revealed lipoid dystrophy of the liver, cloudy swelling of the myocardium and liver, and atrophy of the mucosal glands of the small intestine. *Esch. coli* Type O111B4 was isolated from the bowel, liver, and spleen. The children most susceptible to these pathogenic strains were those aged under 6 months who were already weakened by previous illness or inadequate care, or were suffering from parenteral foci of infection. The treatment should include antibiotic therapy, intravenous infusion of plasma, saline, and glucose, and cardiac restoratives. The intake of vitamins, especially of the B complex, and methionine should be reinforced, and the infants should be treated in strict isolation.

L. Firman-Edwards

1445. **The Rising Incidence of Scurvy in Infants: a Challenge to the Physician and the Community**
W. S. Whelen, D. Fraser, E. C. Robertson, and H. Tomczak. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] **78**, 177–181, Feb. 1, 1958. 1 fig., 22 refs.

The authors review 79 cases of infantile scurvy admitted to the Hospital for Sick Children, Toronto, during the 5-year period 1951–5. Between 1930 and 1953 the average annual incidence of the disease at this hospital was 7 cases, whereas there were 46 cases in 1954 and 25 in 1955.

The clinical findings closely followed the classic pattern. In 90% of cases onset was between the ages of 6 and 12 months, and 50% of the patients showed haemorrhagic tendencies. Rickets was associated with scurvy in only one case. Of 78 patients examined, typical *x*-ray appearances of scurvy were present in 65; the remainder included a few severe cases, but these patients had been ill only a short time. In those cases in which scurvy had not been recognized the patients were initially referred to hospital with a variety of suggested diagnoses, including poliomyelitis, neuritis, rheumatism, congenital dislocation of the hip, leukaemia, anaemia, tumour of the spinal cord, rickets, osteomyelitis, and muscular dystrophy. Infection, especially of the respiratory tract, was present in 45% of cases on admission. The average birth weight of the patients, 50% of whom lived in the city of Toronto, did not differ from that of the general population, but the average weight on admission was 3 lb. (1·36 kg.) below expectation. There was no evidence of a seasonal incidence, but the patients' families contained an average of 3 older children, none of whom had had scurvy. Breast feeding had lasted an average of only 11 days, and no patient was receiving breast milk at the time of diagnosis. In 40% of cases, although the infant had been offered orange juice, this had not been persisted with because of "refusal" or "vomiting"; 80% of the patients had received neither fruit juice nor synthetic ascorbic acid during the 6 weeks before diagnosis. On the other hand 30 infants had received some fruit or vegetables regularly in the diet, while 20% of the parents claimed to have given orange juice or some other source of ascorbic acid in normally adequate amounts. In hospital orange juice and synthetic ascorbic acid were given in combination in an average daily dose of 300 mg. of the vitamin, with a full, mixed diet. No allergic or gastro-intestinal upset occurred, and the response was excellent in all cases.

The authors consider that the increased incidence of scurvy observed in Toronto (though not in Canada as a whole) cannot be attributed to an increase in infantile requirements of ascorbic acid as a result of more rapid

growth or a high incidence of infection. They point out that reconstituted evaporated milk and pasteurized cow's milk, which are most commonly used in Canada for infant feeding, contain only 0·2 mg. and 0·6 mg. of ascorbic acid respectively per 100 ml., as against 5 mg. per 100 ml. of breast milk, and conclude that " in every instance, the scorbutic state must be attributed to an inadequate intake " of the vitamin. They suggest that sociological factors are largely responsible for a deterioration in the dietary care of children, particularly the younger members of families. They deprecate the tendency of physicians to discard orange juice in favour of proprietary vitamin preparations, which parents regard as medicine rather than food. The low incidence of rickets in association with scurvy in their series is probably attributable to the fortification of evaporated milk with vitamin D, and it is recommended that ascorbic acid should also be incorporated during manufacture, with due regard to its instability in non-acid solutions.

[The greater freedom of British infants from scurvy may possibly be attributable to the fact that, so far, evaporated milk is not largely used in Great Britain for infant feeding. Detailed analyses of the social and dietary backgrounds in the authors' cases are not given.]

Pamela Aylett

1446. **Obesity.** [Review Article]
R. S. ILLINGWORTH. *Journal of Paediatrics* [*J. Pediat.*] 53, 117–130, July, 1958. 1 fig., bibliography.

1447. **Management of the Undescended Testis**
J. BRUNET, R. R. DE MOWBRAY, and P. M. F. BISHOP. *British Medical Journal* [*Brit. med. J.*] **1**, 1367–1371, June 14, 1958. 26 refs.

The authors report, from Guy's Hospital, London, the effects of treatment in 209 cases of undescended testis (both testicles in 72 cases and one in 137). In 35 patients first seen when between the ages of 5 and 9 years descent occurred spontaneously before the age of 10; initially 20 of these boys had retractile testes. Of those treated with chorionic gonadotrophin, which stimulates lengthening of the cord, descent occurred in 58% and was more easily brought about the nearer the testis was to the scrotum when the boy was first seen. In respect of position of the testicle, 65·5% of the canalicular, 87% of the retractile, and less than 25% of impalpable testes descended. The optimum dose of gonadotrophin was considered to be 500 units twice weekly for about 6 months.

Surgery was performed when mechanical obstruction was present or after hormonal treatment had proved unsuccessful. In all the cases so treated the testis was brought down into the scrotum, but in follow-up examinations a completely satisfactory anatomical result was found in only 65%. Long-term studies showed that subsequently only 3 of these patients had any gross deficiency of testicular endocrine function, while normal fertility, assessed after 10 years in 53 cases, was present in 27 (93%) of 29 unilateral and in 17 (70%) of 24 bilateral cases. Only one patient treated with chorionic gonadotrophin was infertile.

The authors believe that the ideal age for the treatment of cryptorchism is between 9 and 10 years, since up to this time no severe testicular damage occurs, precocious puberty is avoided, and the operation at that age is technically much easier.

A. Gordon Beckett

1448. **Hydranencephaly (Hydrencephaly)**
L. CROME and P. E. SYLVESTER. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] 33, 235–245, June, 1958. 16 figs., 27 refs.

Hydranencephaly is a congenital condition, not necessarily of uniform aetiology, in which the cerebral hemispheres are replaced by thin sacs containing cerebrospinal fluid (C.S.F.). The lining of the sac consists of pia and arachnoid on the outside and a glial layer on the inside, this being all that remains of the cortical matter. The condition is distinguished, but not always easily, from congenital hydrocephalus by an absence of cranial enlargement and excessive intracranial pressure, by the lack of ependymal lining of the ventricles, and frequently by the absence of any recognizable obstruction in the C.S.F. pathways. The usual name given to the condition suggests a combination of hydrocephalus and anencephaly; but as the latter is not a feature of the abnormality it is suggested that " hydrencephaly " would be a better descriptive name.

Most babies with this condition die within a few months of birth, but the authors present, from the Fountain Hospital, London, the case history and detailed pathological findings in an epileptic idiot with this malformation who survived for 4½ years. Some of the features in this patient were consistent with the diagnosis of congenital toxoplasmosis, but this diagnosis was not verified [in the absence of appropriate tests during life]. Two other cases of hydrocephalus are also described in which the features resembled in some respects those of hydrencephaly. [The paper is profusely illustrated.]

John Lorber

1449. **Major Dysrhythmia or the Flexion-spasm Syndrome.** (La dysrythmie majeure ou syndrome des spasmes en flexion)
R. BERNARD, J. MANASSERO, H. GASTAUT, and A. ROGER. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **34**, 1830–1836, June–July, 1958. 6 figs., 2 refs.

The authors discuss the flexion-spasm syndrome in infancy with reference to 20 cases seen at the Clinique Médical Infantile, Marseilles, supported by an analysis of the recent literature. They list the clinical features as follows. Onset, always during the first year of life, of attacks of flexion of the head, limbs, and trunk, which are always symmetrical and last at the longest for 5 seconds. In rare cases they may be confined to the head and arms, and much more rarely replaced by attacks of extension; they may occur only 2 or 3 times a day or in some cases may be almost continuous; they are usually more frequent at waking and on going to sleep, and are completely unaffected by external stimuli. Sleep may follow an attack, but immediate recovery is more frequent. Severe motor and mental retardation is the usual sequel, though occasionally recovery may be complete. The prognosis

is the more hopeful the shorter the duration of the attacks—which may continue for 2 months to 2 years.

A typical electroencephalogram is described. The waking record between attacks shows diffuse high-voltage delta waves over the entire cortex, on top of which are seen spike waves of an amplitude of 200 to 250 microvolts lasting 0·1 second and frequently followed by post-discharge waves lasting 0·5 second. These last waves are completely irregular both in location and in time, and affect any part of the cortex, though in some cases they may be generalized. During sleep the spike waves tend to occur in bursts and the delta activity has a lower voltage. During an attack there is a sudden and almost complete cessation of electrical activity, the maximum amplitude of waves being 5 microvolts with a frequency of 10 to 25 per second. Other investigations, such as examination of the cerebrospinal fluid, serological tests, and radiography of the skull, have all given negative results. A number of other workers, however, have reported finding dilatation of the ventricles.

The differential diagnosis is discussed briefly. The aetiology would appear to be completely obscure, although in 12 of their 20 cases the authors suspected a congenital abnormality of the brain or birth injury. They also noted an association between the onset of the attacks and whooping-cough in 4 cases, and with vaccination against smallpox in another 4. They suggest that the underlying mechanism of the attacks is a sudden stimulation of the reticular system of the brain stem, but the cause of this stimulation is not known. Treatment with anticonvulsants and prednisone had no effect on the attacks (but in an addendum the authors draw attention to a report by Sorel to a meeting of the Brain Research Foundation of Chicago [no other reference is given] who claimed success with corticotrophin in 3 cases so treated within the first month from onset).

H. G. Farquhar

1450. **The Child Who Refuses to Go to School**
A. Model and E. Shepheard. *Medical Officer* [*Med. Offr*] **100**, 39–41, July 11, 1958. 6 refs.

The authors report, from the Salford and Manchester Child Guidance Clinics, a study of the problem of the child who refuses to go to school, with an analysis of 17 cases and details of 4. The ages of the children ranged from 7 years 10 months to 14 years 4 months, average 11 years 2 months. The I.Q. was above the average in 12 of the 17 children, 10 having an I.Q. of 120 or more; the highest I.Q. was 143, and the mean was 119. The refusal on the part of the children was attributed not to difficulties at school, but to a faulty parent–child relationship which commonly expressed itself on the one hand by over-concern of the parents for the child's physical well-being and on the other by hypochondriacal anxiety in the child. The father was apt to be a shadowy figure at home, playing little part in the child's upbringing. Of the 11 boys in the series, 5 slept with their mothers, although accommodation at home was adequate. The authors state that there was some overlap with truancy, many of the children staying away from school without the parents' knowledge.

R. S. Illingworth

1451. **A Survey of Childhood Malignancies**
A. Stewart, J. Webb, and D. Hewitt. *British Medical Journal* [*Brit. med. J.*] **1**, 1495–1508, June 28, 1958. 1 fig., 18 refs.

An earlier study (Hewitt, *Brit. J. prev. soc. Med.*, 1955, **9**, 81) having revealed an unusual peak of mortality from leukaemia in the 3rd and 4th years of life in recent years, the present survey of fatal malignant disease in childhood was undertaken in the Department of Social Medicine of the University of Oxford with particular reference to the possible influence of modern procedures such as radiology.

An attempt was made to trace all children in England and Wales who had died from leukaemia or other forms of cancer before their tenth birthday during the 3-year period 1953–5, the prenatal and postnatal experiences of these children (the case group) being then compared with those of a control group of healthy children matched for age, sex, and locality. There were 1,694 deaths from leukaemia (792) or other forms of cancer (902) during the period in the age group studied, and the mothers of 1,416 of these children were interviewed by " survey doctors ", who in each case also interviewed the mother of a matched control subject selected at random from the local birth register. Local authorities co-operated, so that the whole country was represented.

The data obtained from death certificates showed that mortality from malignant disease was higher for males than for females and for children under the age of 5 than for older children. The peak mortality from leukaemia was between 2 and 4 years. The results of the survey showed that exposure of the mother to irradiation for diagnostic purposes had occurred more frequently in the case group than in the control group, the ratio being 1·17:1 for all types of examinations at any time before the birth of the child, 1·38:1 for abdominal examinations, and 1·48:1 for examinations during the relevant pregnancy. Other maternal factors which appeared to increase the risk of malignant disease for the child were virus infections during pregnancy, threatened abortion, and excessive maternal age. The effect of postnatal exposure of the infant to *x* rays on mortality from malignant disease appeared to be more marked in respect of leukaemia than other types of cancer, but was much weaker than the effect of prenatal exposure. There was no evidence of a direct relationship between the increase in childhood malignancies and the introduction of new drugs such as sulphonamides and antibiotics, though there may be an indirect relationship, since treatment with these drugs has increased the number of young children who survive acute pulmonary infections, some of whom die subsequently of leukaemia. Studies of the health of the mothers, the feeding habits and home background of the children, and numerous other factors showed no significant differences between the two groups.

The authors' final conclusion is " that foetal irradiation does not account for the recent increase in childhood malignancies, but the finding of a case excess for this event does underline the need to use minimum doses for essential medical *x*-ray examinations and treatments."

I. G. Williams

Public Health

1452. **Disinfection of Drinking Water by the Combined Action of Ultrasonic Radiation and Chemical Disinfectants.** (Обеззараживание питьевой воды при комбинированном действии ультразвуковых волн и малых доз дезинфицирующих веществ)
L. I. ÉL'PINER. *Гигиена и Санитария* [*Gig. i. Sanit.*] **23**, 26–29, No. 7, July, 1958. 3 figs., 8 refs.

This investigation was prompted by the need for an improved method for the disinfection of the drinking-water supply of river steamers, since river water obtained from different places may vary very greatly in chlorine-absorbing power. Reports in the Russian and foreign literature, mainly of a biological or microbiological character, suggested that a hygienic evaluation of the disinfecting properties of ultrasonic radiation would be useful.

With ultrasonic waves at a frequency of 380 kilocycles per second an exposure of 10 minutes or more was required to kill 100% of the organisms in a water layer 5 cm. in thickness infected with *Escherichia coli* (6,800 to 7,560 per ml.). This effect was obtained only with running water. However, the addition of a small concentration of chlorine (0.05 to 0.08 mg. per litre) or of hydrogen peroxide (35 mg. per litre) greatly increased the bactericidal effect of the ultrasonic waves, so that much shorter exposures (3 to 5 minutes) were necessary. It is suggested that changes in the bacterial membrane brought about by ultrasonic irradiation increase the sensitivity of the organisms to disinfectants, and vice versa.

Basil Haigh

1453. **Determination of the Maximum Permissible Concentration of Pyridine in Reservoir Water.** (К обоснованию предельно лопустимой концентрации пиридина в воде водоемов)
S. A. ZJABBAROVA. *Гигиена и Санитария* [*Gig. i. Sanit.*] **23**, 30–35, No. 7, July, 1958. 2 figs., 10 refs.

Pyridine, which is used in the pharmaceutical, leather, and textile industries and is also produced in, and found in the effluent from, coke ovens, coal-tar dye plants, and gasworks, may find its way into reservoir water. It is therefore important to know its effect in small quantities on the self-purification process and on the consumer.

Experiments in model reservoirs showed that pyridine had an inhibitory action on self-purification in a concentration of 1 mg. per litre, whereas 0·5 mg. per litre had only an insignificant effect. A concentration of 2.5 mg. of pyridine per litre was sufficient to give the water a specific intensity of smell of 2 points. The daily administration of pyridine to white rats in a dose of 0.125 or 0.25 mg. per kg. body weight for 100 days caused retardation of growth and disturbance of liver function. In a dose of 0.0125 mg. per kg. it caused no change in the rate of growth of rats or in the rate of development of conditioned reflexes in mice. With a normal water intake this dosage would require a concentration of 0.25 mg. of pyridine per litre, and on the basis of these experiments the author suggests this level as the maximum permissible concentration of pyridine in reservoir water.

Basil Haigh

1454. **The History of Infant Welfare**
B. SOLOMONS. *Journal of Pediatrics* [*J. Pediat.*] **53**, 360–376, Sept., 1958. 24 refs.

EPIDEMIOLOGY AND IMMUNIZATION

1455. **Epidemiology of Stillbirths and Infant Deaths Due to Congenital Malformation**
W. J. R. ANDERSON, D. BAIRD, and A. M. THOMSON. *Lancet* [*Lancet*] **1**, 1304–1306, June 21, 1958. 1 fig., 8 refs.

Statistics of stillbirths and infant deaths occurring among 37,585 single births to patients delivered at the Aberdeen Maternity Hospital during the period 1938–55 and similar statistics relating to all births occurring in the City of Aberdeen during 1949–55 are analysed and compared with certain national data derived from the annual reports of the Registrar-General for Scotland (1939–55). The malformations noted were divided into three categories, namely, anencephalus, other malformations of the central nervous system (C.N.S.), and other malformations. In both local groups it was found that infant mortality and the incidence of stillbirth due to anencephaly and other malformations of the C.N.S. were twice as high as expected among the children of young primiparae, especially those under 20. The only clear excess mortality from other malformations was among the children of mothers aged 35 and more, and was mostly due to mongolism.

While the national statistics for Scotland do not provide comparable information concerning infant deaths due to malformation, they do give the stillbirth rates due to these causes by maternal age and birth-order separately. From these it again appeared that the incidence of anencephalus was relatively high for maternal ages below 20, and also over 35, but that of both other groups of malformations was excessive only at higher maternal ages. Both local and national statistics showed an excess of anencephalus and, to a lesser extent, of other malformations of the C.N.S. in the lower social classes, and the local figures showed a similar excess among the children of women of short stature. For the period 1950–5 the incidence of stillbirths due to all types of congenital malformation was highest in the industrial areas of central and southern Scotland and lowest in the farming areas of the north and west.

The findings of this study suggest strongly that poor social background of the mother predisposes to the risk

of foetal death due to malformation of the C.N.S. The apparent association with low maternal age and short stature is probably attributable to the facts that very few very young mothers come from the higher social classes and that stunted growth is frequently a result of environmental conditions in childhood. These factors, however, may not be the direct cause of malformations, but possibly act by bringing out latent tendencies. As the neural canal of the embryo closes after 4 weeks the remedy obviously cannot lie in improving the mother's living conditions after pregnancy has been diagnosed, but rather in increasing the general prosperity of the lower social classes and securing for them healthier surroundings and a more adequate diet. *M. Maclean*

1456. **Preliminary Report on Mass Vaccination of Man with Live Attenuated Poliomyelitis Virus in the Belgian Congo and Ruanda-Urundi**

G. Courtois, A. Flack, G. A. Jervis, H. Koprowski, and G. Ninane. *British Medical Journal* [*Brit. med. J.*] **2**, 187–190, July 26, 1958. 1 fig., 9 refs.

A trial of the use of attenuated strains of poliomyelitis virus as a live vaccine was carried out in various areas in the Belgian Congo and Ruanda Urundi, 244,596 persons, of whom 103,537 were children under 15, being given the Chat strain of Type-1 poliovirus and 2,511 of them also receiving the Fox-III strain of attenuated Type-3 poliovirus. The vaccines were administered by mouth either in capsules or in liquid form, the approximate minimum dose of each being $10^{5\cdot3}$ TCD_{50} (median tissue culture doses). No sickness was reported following vaccination. A preliminary survey of a random sample of the population of each area before vaccination showed that 12 to 15% had no antibodies against Type-1 and 15 to 43% none against Type-3 virus in the blood. In 4 areas vaccination of the entire population was carried out soon after the outbreak of an epidemic of paralytic poliomyelitis apparently due to Type-1 virus, 8,823 children under 15 and 14,063 adults (included in the totals given above) being given the Type-1 vaccine. No further case of paralysis occurred in any of these areas after the fourth post-vaccination day. In addition to the preliminary surveys large numbers of samples of serum were taken for estimation of antibody content during the trial, and a further report giving more exact details of the susceptibility of the populations vaccinated is promised when the tests are completed.

[It is to be hoped that it was also possible to test samples of faeces, especially of children, before and some weeks after vaccination, particularly in those cases in which the serum was tested.] *W. K. Dunscombe*

1457. **The Epidemiology of the First Poliomyelitis Epidemic (Jamaica) 1954**

L. S. Grant and A. A. Peat. *West Indian Medical Journal* [*W. Indian med. J.*] **6**, 257–271, Dec., 1957 [received June, 1958]. 10 figs., 3 refs.

In 1954 Jamaica experienced its first severe epidemic of poliomyelitis. There had been sporadic cases in earlier years, the highest number reported in any one year between 1930 and 1953 being 13. Before 1944 the disease affected children predominantly; after that year it was frequently seen in adults, suggesting a delay in the development of immunity till later life. In the authors' view this delay in the case of a bowel-borne virus was due to improved sanitation and consequent less risk of immunizing spread of subclinical doses of the virus. The incidence in other Caribbean territories and in the countries of the American continent is briefly discussed.

There were 759 cases of poliomyelitis, mostly paralytic, in Jamaica in 1954, a case rate of 50 per 10,000 population. The case rate was highest in the more thickly populated area of Kingston and the adjoining St. Andrew with its higher standard of living, better medical and hospital facilities, and possibly better notification. The death rate was 6.2 per 100,000. Starting in the urban area of Kingston and the rural area of Clarendon the disease spread rapidly at a rate of 0.8 miles (1·3 km.) a day, and is said to have reached all parishes. The outbreak reached epidemic proportions in the period July to September, the peak incidence being recorded in the last-named month. The age groups mainly affected were young children up to 5 years and young adults aged 20 to 30 years who had presumably grown up without the immunizing benefit of previous exposure to the epidemic strain.

Before the epidemic serological tests for antibodies to poliomyelitis virus of Types 1, 2, and 3 in children and adults indicated an absence of Type 1, but this type was cultured from stool specimens or central nervous system tissue in 9 out of 11 cases during the epidemic, and these showed little heterotypic antibody response. On the basis of the serological findings the authors suggest that the population of Jamaica had been "ripe" for an epidemic of poliomyelitis for several years before 1954 and that the outbreak in that year could be attributed to an increase in virulence of an endemic Type-1 virus in a population whose resistance was lowered by recent widespread epidemics of measles and influenza, or to the entry of a new and more virulent Type-1 virus into the island through extensive movements of population between Jamaica and neighbouring countries. *J. Cauchi*

1458. **Antibody Response following Intradermal or Oral Administration of Formalinised Poliomyelitis Vaccine**

J. H. Connolly, G. W. A. Dick and D. L. Corkin. *Lancet* [*Lancet*] **2**, 333–336, Aug. 16, 1958. 3 figs., 9 refs.

An investigation is reported from the Queen's University, Belfast, into the efficacy of the intradermal (ID) and oral administration of formalinized poliomyelitis vaccine as compared with intramuscular (IM) injection in producing an antibody response in young children. The vaccine used was of the British type, containing the Brunenders, MEF_1, and Saukett strains of poliovirus, and the subjects, all children under 5 years old, received 2 doses of vaccine by one of the three routes at 4 weeks' interval. For ID vaccination each dose of 0.3 ml. was divided into 2 injections of 0.15 ml. given into the skin of the two forearms. The oral dose was 5 ml. given in milk, and the IM dose was 1 ml. Blood specimens were taken for testing by the virus neutralization technique on the day of vaccination and 4 weeks after the second

dose. Altogether 52 children (in 3 separate trials) received ID vaccination, 7 oral vaccination, and 8 IM vaccination.

In the group receiving ID vaccination there were 5 children whose blood initially was without antibody to any of the three types of poliovirus, and 3 of these were still without antibodies 4 weeks after vaccination. Of 7 who were initially without Type-1 antibody only, none developed it within 4 weeks of ID vaccination, but of 34 initially without Type-2 and 36 initially without Type-3 antibodies, 26 and 15 respectively developed these antibodies within 4 weeks. The response of children already possessing antibodies to ID vaccination was more satisfactory, a rise of titre of the three types of antibody being observed in 93%, 82%, and 93% of the cases respectively.

Of 8 children given IM injections, 5 had no Type-1 antibody initially and one had no antibody to any of the types. Four weeks after vaccination only one had produced no Type-1 antibody and all showed a Type-2 and Type-3 antibody response. Of the 7 children given the vaccine orally, 4 showed no antibody response to any type 4 weeks after vaccination; all the others showed a Type-2 antibody response, but Type-1 and Type-3 responses were obtained in only one case each. After each oral dose faecal samples were collected for 10 days to exclude coincidental naturally occurring infection, but no live virus was detected. All the children who failed to respond to ID or oral vaccination were given IM injections later.

The authors conclude that although the response to ID vaccination is poor in children without antibodies to any of the types of poliovirus, a booster response occurs in most children with naturally acquired antibodies. They point out that it has been demonstrated that the initial response is related to the mass of antigen injected; hence the ID route is not to be recommended for primary vaccination. In their opinion oral vaccination has no practical value at present. *W. K. Dunscombe*

1459. **Outbreak of Poliomyelitis in a Small Urban Community**

R. D. Pearce. *Lancet* [*Lancet*] **1**, 1323–1326, June 21, 1958. 1 fig., 3 refs.

An outbreak of poliomyelitis due to Type-1 virus involving 46 notified cases (40 confirmed clinically) in 17 weeks occurred in the spring of 1957 at Brightlingsea, a small, relatively isolated, coast town in Essex with a population of some 4,500. There had been no known case of poliomyelitis in the town up to 1952, and since then only 23 cases had been notified. The first case in the present outbreak, in a 4½-year-old boy, occurred in January, 1957, at a time when no other known case of poliomyelitis existed in east Essex, but 2 days after the boy's discharge from hospital in March 2 further cases were notified and from then until the beginning of June 37 further cases were confirmed, 6 being in adults. The disease appeared to spread in a narrow channel either by droplet infection or by faecal contamination, there being evidence of a chain of contacts between infected households. In 9 households 2 or more cases occurred. The probable shortest incubation period in different cases ranged from 5 to 18 days.

Of the 40 cases, 24 were paralytic, but only 3 patients subsequently required treatment in an orthopaedic hospital. An " invasion stage " marked by pyrexia, headache, and coryza, occurred in 28 of the 40 patients before the onset of meningeal signs and symptoms. Of 13 children in Brightlingsea who had been vaccinated in 1956 against poliomyelitis, none showed any symptoms of the disease, although several had been in very close contact with confirmed cases. Serological evidence of recent infection was found in several of these children as well as in other school contacts. *A. Ackroyd*

1460. **Antibodies against Poliovirus in Vaccinated and Unvaccinated Children in an Epidemic Area**

G. P. B Boissard. *Lancet* [*Lancet*] **1**, 1326–1328, June 21, 1958. 18 refs.

A month after the end of the outbreak of poliomyelitis at Brightlingsea in the spring of 1957 [described in Abstract 1459] a blood sample was obtained from each of the 13 children who had received 2 doses of poliomyelitis vaccine in the early summer of 1956 and, in 9 cases, compared with the blood from 9 unvaccinated local children aged 3 to 9 of similar age and sex in respect of neutralizing and complement-fixing antibody levels. Except for one of the unvaccinated children, none of the children in either group had caught the disease.

Neutralizing antibody to Type-1 virus was found in the serum of 6 of the unvaccinated children and to Type 2 in one, but no antibody to Type 3 was found; 5 of the 6 sera with Type-1 neutralizing antibody also fixed complement with Type-1 virus. The sera of most of the vaccinated children had neutralizing antibody to all 3 types in high titre. In the sera of 7, however, the titre of neutralizing antibody to Type-1 virus was higher than might have been expected a year after vaccination, and it appeared that antibody response had been reinforced in these children by an infection with Type-1 virus which had had a similar effect to that produced by a third dose of vaccine. These 7 sera reacted positively with Type-1 virus in the complement-fixation test, although the titres in 2 cases were low, while 5 of them fixed complement with Type-2 virus and 4 also gave a heterologous reaction with Type-3 virus. High neutralizing antibody titres to Type 2 in one case and to Type 3 in another suggested that natural infections with these 2 types had occurred either before or after immunization. In one serum sample heterologous complement-fixing antibody to Type-3 virus was present in the absence of neutralizing antibody at a dilution of the serum of 1:8.

The results indicate that, provided paired sera are obtained from immunized children, the complement-fixation test is still of value in the diagnosis of poliomyelitis infections in children who have had 2 doses of vaccine, since the homologous complement-fixing antibody titre rises more rapidly than the heterologous. Recent trials on sera obtained a fortnight after a third dose of vaccine, however, suggest that this test is of little or no value in diagnosing subclinical poliomyelitic infections during this period. *A. Ackroyd*

Industrial Medicine

1461. **Pneumoconiosis in Iron Miners.** (La pneumoconiose des mineurs de fer)
R. Even and C. Sors. *Presse médicale* [*Presse méd.*] **66**, 906–907, May 21, 1958. 6 figs.

The authors describe the findings at post-mortem examination in 12 Lorraine iron-ore miners, in whom there was radiological evidence of pneumoconiosis. Of these men 7 had died from right ventricular failure, one from tuberculosis, and 4 from miscellaneous conditions. In every case there was an excess of iron in the lung, and the silica content was raised in 6 with histological evidence of silicosis. Emphysema and non-specific fibrosis were observed in all cases. It is concluded that this form of pneumoconiosis should be scheduled as an occupational disease. *C. M. Fletcher*

1462. **An Epidemiological Study of Lung Cancer in Asbestos Miners**
D. C. Braun and T. D. Truan. *A.M.A. Archives of Industrial Health* [*A.M.A. Arch. industr. Hlth*] **17**, 634–653, June, 1958. Bibliography.

From a review of the literature the authors conclude that the evidence of an association between cancer of the lung and asbestosis is insufficient to prove that a causal relationship exists between the former disease and exposure to asbestos dust. Fresh data were therefore obtained by studying the clinical records of 6,091 miners who had been employed in the asbestos industry in the Province of Quebec for 5 years or more and who were on the employment roll in 1950; office and other workers not exposed to dust were excluded. The men were followed up to the end of 1955, by which time 187 had died and 133 had been lost sight of. Among the 187 deaths, 9 were considered to have been definitely due to primary cancer of the lung, while in a further 3 cases lung cancer was suspected to be the cause of death, but the exact diagnosis remained in doubt. The annual death rate from lung cancer among these miners (25 per 100,000, or 34 per 100,000 if the suspected cases are included) was only slightly higher than that recorded for the Province as a whole among all adult males over the same period (23 per 100,000). Analysis of the rates by age showed broadly similar results for all age groups, and classification of the miners according to the degree of exposure to dust showed the rates to be similar whether exposure was light, moderate, or heavy. The mortality increased with length of employment up to 40 years, but decreased thereafter. The smoking habits of nearly all the miners were known from their clinical records, and it was found that all the deaths from lung cancer occurred among the 79% of miners who usually smoked more than 5 cigarettes a day.

It is concluded that " the asbestos miners in the Province of Quebec do not have a significantly higher death rate from lung cancer than do comparable segments of the general population ". Asbestosis was found in 4 of the 8 proved cases of cancer of the lung which came to necropsy, but the epidemiological findings, and especially the observation that mortality did not increase consistently with duration or degree of exposure, are regarded as " strong evidence against the carcinogenicity of asbestos ".

[It may be noted that the asbestos mined in the area studied is chrysolite, whereas the type most commonly associated with asbestosis is hornblende.]

Richard Doll

1463. **Anthrax and Bone-meal Fertiliser**
D. M. Green and W. M. Jamieson. *Lancet* [*Lancet*] **2**, 153–154, July 19, 1958. 4 refs.

Over a period of 6 years 10 cases of anthrax have been admitted to King's Cross Hospital, Dundee, of which 6 have already been reported by the authors (*Lancet*, 1955, **2**, 560). In the present paper 4 further cases are described, the condition in 3 being directly attributable to the handling of infected bone-meal products imported from India and the Argentine. A boy aged 15 with anthrax of the left cheek had been using bone fibre for preparing soil. A malignant pustule developed 10 days after he had scratched his face. The condition cleared up completely after a course of treatment with penicillin and streptomycin. Antibiotic therapy was also successful in two farm workers with cutaneous lesions.

Bacillus anthracis was isolated from samples of bone-fibre handled by the first patient. The material was shaken up with distilled water, and after 2 hours the supernatant fluid was heated to 70° C. for 10 minutes and then poured on plates of " yeastrel " agar. Deep colonies of the organism were isolated. A portion of the supernatant fluid was centrifuged and the deposit was injected into guinea-pigs. Within 72 hours the animals showed the typical macroscopical and microscopical appearances of anthrax. Strains of the organism were found to be sensitive to penicillin, streptomycin, chlortetracycline, oxytetracycline, and erythromycin.

A. Garland

1464. **The Early Clinical Effects of Ionizing Radiations on the Body.** (К клинике начальных стадий хронического воздействия на организм ионизирующего излучения)
E. A. Drogičina, N. K. Bjalko, I. A. Gel'fon, N. I. Ivanov, M. A. Kazakevic, T. B. Linevič, B. G. Osipova, B. I. Stepanova, M. N. Ryžkova, E. A. Solov'eva, and L. G. Centerova. *Гигиена Труда и Профессиональные Заболевания* [*Gig. Truda prof. Zabolev.*] **2**, 3–8, No. 2, March–April, 1958. 18 refs.

In this paper from the Institute of Industrial Hygiene and Occupational Diseases of the Academy of Medical Sciences of the U.S.S.R. the authors describe the results of 3 years' routine medical examinations of workers ex-

posed to ionizing radiations, both in scientific work and in industry. They found that the great majority of those examined, who had been in contact with ionizing radiations for one to 5 years, remained healthy. Only a few complained of symptoms which could be attributed to radiation, these usually being persons who were exposed to a broad spectrum of radiation.

The most common physical findings in the initial stage of chronic radiation sickness were: (1) changes suggesting disorders of haematopoiesis—reticulocytosis, increased bleeding time, and a tendency towards leucopenia with a relative lymphocytosis and a shift to the left; (2) changes in vascular permeability; (3) metabolic disorders—dissociation of the serum protein fractions, an increase in the histamine and a reduction in the chloride content of the blood, and suppression of cholinesterase activity; and (4) functional changes in the nervous system. These last were usually of the asthenic or neurotic type, but were sometimes associated with polyneuritis. The most serious cases were characterized by persistent vasomotor disorders. A marked variation in individual susceptibility to radiation was noted. Intensification of the programme of medical supervision of these workers and of study of their working conditions is recommended.

Basil Haigh

1465. **Blood Pressure Levels and the Incidence of Hypertension in Rubber Workers.** (Уровень артериального давления и распространенность гипертонической болезни у рабочих резиновой промышленности)
N. K. Beljaeva. *Гигиена Труда и Профессиональные Заболевания* [*Gig. Truda prof. Zabolev.*] **2**, 8–12, No. 2, March–April, 1958. 3 figs., 7 refs.

Workers in the rubber industry are exposed to a variety of potentially toxic substances, the most important being benzene. There are conflicting reports in the literature of the effect of benzene on the blood pressure, and this paper describes the results of an investigation carried out among workers at two rubber factories.

It was found that workers in departments in which the working atmosphere contained benzene had a lower average arterial pressure than control subjects, irrespective of the type of work performed. The incidence of hypertensive disease among workers in contact with benzene was found to be only about half that among workers not handling benzene (2.7% and 5.9% respectively), with the exception of operatives making goloshes, among whom the incidence was 5.6%. This last finding, however, may result from some other factor in the working conditions of this particular department, benzene itself exerting a hypotensive action.

Basil Haigh

1466. **Clinical Features of Acute Phenylhydrazine Poisoning.** (К вопросу о клинике острой интоксикации фенилгидразином)
A. A. Orlova and N. N. Šatolov. *Гигиена Труда и Профессиональные Заболевания* [*Gig. Truda prof. Zabolev.*] **2**, 12–16, No. 2, March–April, 1958. 4 refs.

Phenylhydrazine is widely used in the pharmaceutical industry, but although experimental work has been carried out on its toxic action on animals, reports of its effects on man are almost non-existent. This paper describes 2 cases of acute phenylhydrazine posioning occurring in workers at a factory producing amidopyrine.

The first patient, a woman of 24, accidentally spilled phenylhydrazine on her hands. The next day she complained of severe headache, weakness, nausea, vomiting, and a dark colour of the urine, and on the third day she developed jaundice and was admitted to hospital. The skin and mucous membranes were pale. The palms of the hands and the nails were yellow (xanthoprotein reaction). The liver and spleen were moderately enlarged and tender. The heart was normal in size, with an apical systolic murmur. Severe anaemia was present, the erythrocyte count being 1,750,000 per c. mm., haemoglobin content 6 g. per 100 ml., and reticulocyte count 20%. Liver function tests gave normal results. In the second case the symptoms appeared gradually over a period of 7 months, although the patient had worked in the factory on the same process for 12 years. The clinical features were similar.

The condition was essentially a haemolytic anaemia, and it was attributed to phenylhydrazine rather than other compounds concerned in the process because of the history in the acute case and the occurrence of an identical condition in the second patient exposed to the same environment, and because of the absence of the methaemoglobinaemia which is associated with poisoning by such agents as aniline and sodium nitrate. *Basil Haigh*

1467. **Hygienic Standard of Produce Grown in Soil Treated with Hexachlorane.** (Гигиеническая оценка продовольственных культур, выращенных на почве, обработанной гексахлораном)
N. M. Rusin, G. P. Andronova, I. N. Sapronova, and O. I. Vasil'eva. *Гигиена и Санитария* [*Gig. i. Sanit.*] **23**, 32–36, No. 6, June, 1958

An investigation is reported into the toxicity and palatability of crops and vegetables grown in soil treated before sowing with various quantities of hexachlorane, with and without its γ-isomer. The maximum dose of hexachlorane used was 400 kg. per hectare in the form of a 12% dust. It was found that wheat and potatoes grown under these conditions contain breakdown products of hexachlorane, but no toxic effects were observed on feeding such crops to rats and mice. The addition of the γ-isomer in different quantities had no significant effect on the results.

As a rule potatoes grown on soil treated with hexachlorane have an unpleasant taste which renders them inedible, whereas starch prepared from such potatoes does not have this taste, nor is it present in wheat grown in the same soil, though grain contains 10 times as much residual hexachlorane as potatoes. The authors therefore advise that land treated with hexachlorane should be sown with cereals for the first 3 or 4 years; only after this period should it be used for growing potatoes.

Basil Haigh

1468. **Threshold Limit Values for 1958**
American Conference of Governmental Industrial Hygienists. *A.M.A. Archives of Industrial Health* [*A.M.A. Arch. industr. Hlth*] **18**, 178–182, Aug., 1958.

Forensic Medicine and Toxicology

1469. **Suicide, Homicide, and Wounding with the Humane Killer.** (Suicide, Tötungen und Verletzungen durch Viehschussapparate)
G. SIMON. *Archiv für Psychiatrie und Nervenkrankheiten* [*Arch. Psychiat. Nervenkr.*] **197**, 124–147, 1958. 4 figs., 11 refs.

This is a very detailed and thorough report from the Surgical Clinic of the University of Würzburg of 23 cases in which death or injury was caused by the discharge of a humane killer. In addition, the author mentions another 15 cases found in the literature. [See also Obersteg and Megglin, *Schweiz. med. Wschr.*, 1958, **88**, 163; *Abstr. Wld Med.*, 1958, **24**, 156.]

The 23 victims in the author's series were all males and all had access to, and were familiar with, the use of the weapon, which in all cases was of the captive-bolt type. Full details are given of 8 cases of successful and 3 of attempted suicide and of 3 fatal and 4 non-fatal cases of accidental injury, while another 5 fatal suicidal cases are summarized. The marked occupational association is emphasized. In all the suicidal cases the wound was in the head, the injuries being very severe. The punched-out nature of the wound with its " precursory " charge of skin and splintered bone is described, and operation, *x*-ray, and necropsy findings are detailed. The need for meticulous wound toilet even in its depths is emphasized; in one case a portion of the wall of the frontal sinus was found in the brain below the corpus callosum at a depth of 9 cm., the patient ultimately recovering.

After surveying the cases reported in the literature the author discusses various factors, such as age, sex, psychological considerations, and motive, which might determine the choice of this method for suicide. Of the 26 persons committing or attempting suicide in the combined series, only 2 were females and both were psychotic, whereas only 5 of the males were psychotic. Of 4 cases of homicide found in the literature, 2 were deliberate and 2 due to negligence. All the accidental injuries occurred when the victim was at, or preparing for, work and there is no mention of the " didn't know the gun was loaded " type of accident.

W. K. Dunscombe

1470. **Toxic Encephalopathy Due to " Stalinon ".** (Encéphalopathies toxiques au stalinon)
P. COSSA, —. DUPLAY, —. FISCHGOLD, —. ARFEL-CAPDEVIELLE, —. LAFON, —. PASSOUANT, —. MINVIELLE, and J. RADERMECKER. *Revue neurologique* [*Rev. neurol.*] **98**, 97–108, Feb. [received July], 1958.

The authors give a detailed description of 11 cases of " stalinon " poisoning [see Abstract 1472], in 9 of which electroencephalographic observations were made. Gross but variable changes were seen in the tracings which the authors interpreted as evidence of a toxic encephalopathy. In some cases these changes persisted without clinical signs for as long as 4 months after the original illness. Six of these patients died, and necropsy was performed on 4 of them. Macroscopically, the brain was oedematous and congested and there was also some congestion of the kidneys, lungs, and myocardium. Microscopically, there was gross interstitial oedema of the neuraxis, with widespread damage to the nerve cells and their processes as well as changes in the glial elements. Little vascular damage was found.

H. B. Stoner

1471. **Nervous Lesions Due to Ingestion of an Ethyl Tin Compound (" Stalinon ").** (Lésions du névraxe secondaires à l'ingestion d'éthylétain (stalinon))
J. E. GRUNER. *Revue neurologique* [*Rev. neurol.*] **98**, 109–116, Feb. [received July], 1958. 6 figs., 3 refs.

The author describes the pathological changes found in the nervous system in 4 fatal cases of " stalinon " poisoning [see Abstract 1472] and compares them with the appearances seen after experimental poisoning in monkeys and mice. The changes were the same in all three species, the dominant feature being gross interstitial oedema of the white matter. Some changes were also seen in the nerve cells and their axons, but they were not so marked as in the macroglia and there was no Wallerian degeneration. The microglia was normal, as were also the cerebral arteries, but venous stasis was prominent. Endothelial proliferation was seen in the smaller veins and thrombosis was present in some of them. Small perivenous haemorrhages were found in some areas. The author compares these findings with those in other forms of cerebral oedema. Although there are similarities, he concludes that the lesions of alkyl tin poisoning have certain characteristic features

H. B. Stoner

1472. **A Clinical Survey of 210 Cases of Intoxication by Organic Salts of Tin.** (Étude clinique d'ensemble de 210 cas d'intoxication par les sels organiques d'étain)
T. ALAJOUANINE, L. DÉROBERT, and S. THIÉFFRY. *Revue neurologique* [*Rev. neurol.*] **98**, 85–96, Feb. [received July], 1958.

The authors analyse the clinical findings in 201 out of 210 cases of alkyl tin poisoning, 98 of which were fatal, following the use of a proprietary medicine, " stalinon ", which contained diethyl tin diiodide as the main ingredient, together with monoethyl and triethyl tin as impurities.

Severe headache was the most constant symptom, being absent in only 3 cases. Vomiting was also very frequent (146 cases), but was not often projectile. Other symptoms were abdominal pain (19 cases), constipation (31 cases), vertigo (37 cases), and urinary retention (46 cases). Many patients complained of visual disturbances, the commonest being photophobia. There was a notable absence of pyrexia, fever being reported only in

12 cases in which there was evidence of coexisting infection, while in 12 cases the body temperature fell (minimum 34° C.). There was rapid loss of weight. Psychic disturbances were very common and provided one of the best indications of the severity of the case. The sleep rhythm was disturbed. Coma supervened in the fatal cases, lasting several hours or days. Asthenia was a frequent and persistent complaint, while convulsions occurred in 23 cases.

Despite the severity of the symptoms, physical signs were often completely absent, even in 51 of the fatal cases. Moderate clinical signs of meningism were found in 75 cases. Transitory pareses lasting 5 to 6 hours occurred fairly frequently, and more permanent paralysis of one or more limbs was found in 35 cases. Very occasionally there was a cranial nerve palsy. The optic fundus was examined in 111 cases, but in 73 it was normal —even in 38 out of 48 fatal cases. In the remaining cases there was some degree of papilloedema. The composition of the cerebrospinal fluid was usually normal. (The pressure is not recorded.) The authors comment that it is interesting that although the condition is now known to be associated with generalized massive cerebral oedema, lumbar puncture was performed in these cases without untoward incident. Electroencephalograms were obtained on 40 occasions and a variety of changes seen, but nothing to suggest a local lesion.

When recovery occurred progress was slow, and in some cases it was 10 months before the patient could return to work. There were permanent sequelae in 24 cases. In 6 of these there was severe flaccid paraplegia, loss of sensation, and incontinence. Persistent external ocular palsies were also seen, with diminution of visual acuity. Various psychic disturbances also persisted after physical recovery.

In 38 of the fatal cases the patient died in coma, in 8 during convulsions, and in 20 as a result of " syncope ". The remainder died of respiratory failure. No medical treatment was of any avail, the only procedure which gave any striking benefit being surgical decompression.

H. B. Stoner

[This issue of the journal contains four more short papers on cases of alkyl tin poisoning—EDITOR.]

1473. **Toxicity of Diacetyl Monoxime and of Pyridine-2-aldoxime Methiodide in Man**

B. V. JAGER and G. N. STAGG. *Bulletin of the Johns Hopkins Hospital* [*Bull. Johns Hopk. Hosp.*] **102**, 203–211, April, 1958. 2 figs., 10 refs.

The potential toxicity for man of two oxime drugs—diacetyl monoxime (2-oximino-3-butanone; DAM) and pyridine-2-aldoxime methiodide (2-oximinomethyl n-methyl pyridinium iodide; PAM), both of which are known from animal experiments to be effective antidotes to certain organic phosphorus cholinesterase inhibitors—has been investigated at the University of Utah College of Medicine, Salt Lake City. Each drug was dissolved in isotonic saline solution in a concentration of 30 to 40 mg. per ml. and administered intravenously to 11 medical-student volunteers in doses of 15 to 30 mg. per kg. body weight, the period of injection varying between 2 and 4 minutes. DAM was also given to 8 and PAM to 6 ward patients.

DAM caused pain along the vein on injection, which subsided within a minute, and a bitter taste in the mouth lasting up to 30 minutes. A number of the subjects experienced tingling sensations for 3 to 5 minutes, and others complained of lightheadedness or dizziness. Of 6 subjects given 30 mg. of DAM per kg., 5 became comatose for up to 10 minutes and one developed a generalized clonic convulsion. This dose was also found likely to cause electroencephalographic abnormalities. There was no nystagmus or impairment of accommodation. The injection of 20 mg. of DAM into the brachial artery of 2 subjects in whom sweating of the hands was observed was followed, after transient discomfort throughout the arm, by cessation of the sweating for a period of 20 to 30 minutes.

After the administration of PAM the commonest complaint was a feeling of dizziness which began during the injection and continued for as long as 45 minutes thereafter. Other symptoms were blurred vision, diplopia, headache, impaired accommodation, and nausea. The preparation of PAM used was found to be contaminated with small amounts of pyridine-2-aldehyde.

There was no evidence of immediate or delayed injury to haematopoietic tissue, liver, kidneys, or cardiovascular system with either drug. *Norval Taylor*

1474. **Use of Oximes in the Treatment of Intoxication by Anticholinesterase Compounds in Normal Subjects**

D. GROB and R. J. JOHNS. *American Journal of Medicine* [*Amer. J. Med.*] **24**, 497–511, April, 1958. 9 figs., 32 refs.

The oximes, pyridine-2-aldoxime (2-PAM) and diacetyl monoxime (DAM), protected against the inhibition of human cholinesterase enzymes by organophosphorus and quaternary ammonium anticholinesterase compounds *in vitro*, and 2-PAM reversed this inhibition. The oximes reversed neuromuscular block and plasma and red blood cell cholinesterase inhibition produced in normal subjects by the administration of " sarin ", neostigmine, bis-neostigmine, pyridostigmine, bis-pyridostigmine and ambenonium. The intravenous dose required to alleviate generalized weakness was 1,000 to 2,000 mg. These doses did not relieve the muscarine-like effects of the anticholinesterase compounds, and their influence on central neural effects was not pronounced. DAM produced local burning and mild systemic symptoms. 2-PAM produced a transient, local neuromuscular block following the intra-arterial injection of high concentrations. This was enhanced by the prior injection of anticholinesterase compound.

2-PAM and DAM are valuable adjuncts to atropine in the management of anticholinesterase intoxication, and should diminish the necessity for, or duration of, artificial respiration and endotracheal intubation.—[Authors' summary.]

1475. **Subsequent Mental Development of Children with Lead Encephalopathy, as Related to Type of Treatment**

J. E. BRADLEY and R. J. BAUMGARTNER. *Journal of Pediatrics* [*J. Pediat.*] **53**, 311–315, Sept., 1958. 8 refs.

Anaesthetics

1476. **A Comparison of Artificial Ventilation and Spontaneous Respiration with Particular Reference to Ventilation–Bloodflow Relationships**
E. J. M. CAMPBELL, J. F. NUNN, and B. W. PECKETT. *British Journal of Anaesthesia* [*Brit. J. Anaesth.*] **30**, 166–175, April, 1958. 1 fig., 20 refs.

A study, by refined methods of respiratory physiology, into the effects of positive-pressure breathing on ventilation and perfusion has been carried out at the Middlesex Hospital and the Royal College of Surgeons of England, London, on 6 subjects in whom the relationship of ventilation to perfusion was measured first when they were conscious and then when they were anaesthetized and receiving artificial respiration. The study involved measurements of volume and composition of the expired air, of the oxygen and carbon dioxide tensions of the arterial blood, and of the CO_2 content of the plasma. From these measurements the dead space and the alveolar–arterial CO_2 tension difference could be calculated. A considerable increase in dead space occurred during artificial respiration, suggesting that the pattern of ventilation produced by positive-pressure respiration is less efficient than that of natural breathing.

Ronald Woolmer

1477. **Potential Deadspace in an Anaesthetic Mask and Connectors**
A. D. CLARKE. *British Journal of Anaesthesia* [*Brit. J. Anaesth.*] **30**, 176–181, April, 1958. 7 figs., 10 refs.

The author, working at the University of Bristol, has measured the dead space under a normal anaesthetic facepiece with an inflatable cushion. The measurements were made on 45 cadavers, different pressures being applied by a Connell harness and with the cushion inflated to different tensions. The dead space was found to vary between 75 and 110 ml. The dead space in several types of connector was also measured: the commonly used " elbow-joint " was shown to contain about 30 ml. Thus it appears that the use of a conventional facepiece and connector may double the respiratory dead space and result in hypercapnia. *Ronald Woolmer*

1478. **Blood-pressure under Anaesthesia in the Sitting Position**
V. GOLDMAN, W. B. CORNWELL, and V. R. E. LETHBRIDGE. *Lancet* [*Lancet*] **1**, 1367–1368, June 28, 1958. 3 figs., 1 ref.

It has been suggested by Bourne (*Lancet*, 1957, **2**, 499; *Abstr. Wld Med.*, 1958, **23**, 66) that hypotension may occur during nitrous oxide anaesthesia with the patient in a sitting position as for dental extraction, and that in such circumstances the maintenance of the upright posture may cause delayed recovery and possibly brain damage. The present authors therefore investigated changes in the blood pressure occurring during general anaesthesia for out-patient dental treatment in 100 unselected cases at the Eastman Dental Hospital, London. The patients' ages ranged from 5 to 65 (median 15) years and the duration of anaesthesia ranged from 1 to 18 (median 3) minutes. The method of anaesthesia was that used as a routine at the hospital for many years. No premedication was given and induction was begun with 100% nitrous oxide until the respiration became automatic. Thereafter oxygen was given, the concentration starting at 8% and rising by approximately 1% per minute. The patient sat upright in the chair with the head in the " sniffing " position. The blood pressure was measured at short intervals throughout the period of anaesthesia and twice after recovery. [No details are given of the method by which the measurements were made.]

In 94 cases the systolic blood pressure rose above the pre- and postoperative levels at some time during anaesthesia. In 21 of these cases, after an initial rise, a fall occurred when oxygen was introduced into the inspired gas mixture, but in none did the level fall below the postoperative reading. Induction was accompanied by a fall in blood pressure below the preoperative level in 9 cases, but it was noticed that these patients tended to be excitable or nervous, and that the pressure during anaesthesia never fell below the postoperative level. At the end of anaesthesia the blood pressure fell usually 5 to 10 mm. Hg below the preoperative level. [No details are given, however, of the extent of the fall in those cases in which it was greater than the mean value; nor was any attempt made to correlate the extent of the fall with the recovery time.]

The authors conclude that the frequency with which syncope occurs under nitrous-oxide–oxygen anaesthesia in the sitting position is insufficient to cause great alarm. They hope that the results of their investigations " will be accepted as proof that no special risk attends the routine that has been used for so many years, provided that nitrous oxide and oxygen are the sole anaesthetic agents used ". *J. F. Nunn*

1479. **Elimination of Carbon Dioxide**
P. N. PETERSEN and J. O. ELAM. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **37**, 91–106, May–June, 1958. 4 figs., 14 refs.

The authors, working at Roswell Park Memorial Institute, Buffalo, New York, made continuous measurements of the total expiratory volume and of either the alveolar or the average expired concentration of carbon dioxide in 27 healthy adults due to undergo comparatively minor operations. Control readings were first made with the patient breathing either oxygen or air and the procedure was then repeated during anaesthesia. The patients were divided into four groups who were anaesthetized respectively with: (1) pethidine–nitrous-oxide–oxygen; (2) pentobarbitone–nitrous-oxide–oxygen; (3)

thiopentone–pethidine–nitrous-oxide–oxygen; and (4) nitrous-oxide–oxygen–ether. The concentration of inspired oxygen was kept at 30 to 35%. Anaesthesia was maintained at Stage III, Plane 1, and respiration was not assisted.

The output of CO_2 was diminished during anaesthesia in the first three groups and increased in Group 4. The authors consider that pethidine and pentobarbitone should not upset CO_2 homeostasis if they are given in correct dosage. However, when a combination of thiopentone and pethidine is employed respiration should be assisted in order to avoid CO_2 retention. Increased alveolar ventilation is also required with ether anaesthesia. *Mark Swerdlow*

1480. **Hypotensive Response to Carbon Dioxide. The Influence of Carbon Dioxide on the Blood Pressure Response of Cats to Hypotensive Drugs**
J. P. PAYNE. *Anaesthesia* [*Anaesthesia*] **13**, 279–288, July, 1958. 7 figs., 13 refs.

In an investigation carried out at the Royal College of Surgeons of England on anaesthetized cats the arterial blood pressure was recorded continuously and the effect determined of the administration of 5, 10, and 20% carbon dioxide, each concentration being given for 5 to 10 minutes. Each animal then received in succession hexamethonium, mecamylamine, and trimetaphan by intravenous injection. After the administration of each drug the blood-pressure response to the three concentrations of CO_2 was again recorded, an interval being allowed for stabilization between each stimulus. The author also studied the effects of CO_2 inhalation on the blood pressure of cats which had been given an intrathecal injection of procaine.

In normal cats the inhalation of CO_2 caused a marked, maintained rise in blood pressure, a sharp fall to subnormal levels following its discontinuation. In cats which had received mecamylamine and in those given intrathecal procaine CO_2 caused marked hypotension. After hexamethonium and trimetaphan had been given, however, CO_2 caused a slight transient fall in blood pressure followed by a hypertensive response. It is suggested that if all vasomotor impulses are effectively blocked (as with mecamylamine and intrathecal procaine) CO_2 will have a peripheral action only, with resulting hypotension. *Mark Swerdlow*

1481. **Hypothermia Using Air Cooling**
A. C. FORRESTER. *Anaesthesia* [*Anaesthesia*] **13**, 289–298, July, 1958. 5 figs., 13 refs.

The author details the physiological and physical factors governing heat balance. He then goes on to describe a method of producing hypothermia which he has used satisfactorily on 11 patients undergoing cardiac surgery at Glasgow Royal Infirmary.

The patient receives promethazine and pentobarbitone on the night before operation, and promethazine, pethidine, and scopolamine on the morning of the operation. Anaesthesia is induced with a sleep dose of thiopentone, followed by nitrous-oxide–oxygen supplemented with intermittent injections of pethidine. Curare is given to produce apnoea and the respiration is controlled throughout, moderate hyperventilation being employed. After induction of anaesthesia the patient is placed in a cabinet (the design and construction of which are described in detail) through which cold air at −5° C. is circulated, the patient's temperature being recorded at 5-minute intervals. Cooling is stopped when the temperature reaches 1·5° to 3° C. above the level at which the operation is to be performed and the patient is then transferred to the operating table. The average time for cooling is 1½ hour in adults and 1 hour in children. After the operation the patient is replaced in the cabinet and warmed to 34° C. by circulating air at a maximum of 45° C. before being returned to the ward. Two detailed case histories are appended. *Mark Swerdlow*

1482. **Deep Hypothermia in Brain Surgery.** (L'hypothermie profonde en chirurgie cérébrale)
G. VOURC'H, G. ARFEL, G. GUIOT, and J. ROUGERIE. *Anesthésie et analgésie* [*Anesth. et Analg.*] **15**, 38–77, Jan.–Feb. [received July], 1958. 10 figs., bibliography.

This paper describes the technique of deep hypothermia employed by the authors at the Centre Medico-Chirurgical Foch, Suresnes, Seine, for operations on the brain and gives a detailed account of its use in 3 cases. This is preceded by a review of previous work [which is well worth reading in full]. The cerebral blood flow at normal temperatures is stated to be 50 ml. per 100 g. brain substance per minute, and cerebral oxygen consumption 3.3 ml. per 100 g. per minute. The latter figure can be reduced by means of barbiturates to 2·1 ml. per 100 g. per minute, but the authors stress the importance of thinking in terms of oxygen need rather than oxygen consumption, and suggest that the use of non-volatile drugs to depress cerebral metabolism is undesirable for brain surgery under hypothermia. They discuss the experimental evidence of the subtle damage which cerebral anoxia may cause and of the protection from it which hypothermia may afford, at any rate in dogs. They point out, however, that there are considerable differences in the anatomy of the cerebral vessels in different species, and they go on to consider, with illustrative case histories, the extent to which vascular occlusion in man can be compensated for by collateral flow from neighbouring blood vessels. Experience has shown that general anaesthesia, though it may diminish the oxygen consumption of the body as a whole, does not increase the tolerance of the brain to vascular occlusion, and hypothermia is the only practical method by which this tolerance may in fact be increased. They aim to reduce the body temperature to 25° to 27° C., at which level the metabolism of the brain is decreased by about 30% and oxygen demand is reduced in proportion. The intracranial pressure is also decreased, which is a considerable advantage.

The authors use a bath of cold water to achieve hypothermia, the patient being supported in it on a hammock. They do not use relaxants to control shivering, relying solely on ether, because they regard natural respiration as a guide which must be preserved. Moreover, ether has

the advantages of rapidity and controllability of action, with the production of vasodilatation. Changes in the electrocardiogram during hypothermia are trivial. It is not always easy to separate the effects of anaesthesia from those of hypothermia on the electroencephalogram, but the typical effect of cooling is to increase the frequency of the dominant rhythm to about 19 c.p.s. Bilateral clamping of the carotid arteries in one of the authors' cases resulted in the temporary superposition of theta rhythm at 6 c.p.s.

They conclude by emphasizing that although considerable advantages are to be gained from the use of hypothermia in neurosurgery and the technique may make cure possible in a number of otherwise inoperable cases, it is nevertheless not without risk, and its use should be confined to those cases which cannot be treated by conventional means. *Ronald Woolmer*

1483. **The Effect of Tensilon on Prolonged Apnea after Use of Succinylcholine**

H. L. ENGEL, S. I. JOSEPH, and J. S. DENSON. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **37**, 87–90, May–June, 1958. 12 refs.

Investigations were carried out at Los Angeles County Hospital during operation on 50 patients, each of whom had been receiving a continuous drip infusion of 0·1% succinylcholine either for a period of at least 2 hours or to a total dosage of 500 mg. Each patient was rendered apnoeic by increasing the rate of infusion and kept apnoeic for at least 5 minutes. The infusion was then stopped and the time of recommencement of respiration and that of recovery of clinically adequate respiratory effort were noted. The experiment was then repeated, but as soon as respiration had restarted 10 mg. of "tensilon" (edrophonium chloride) was injected intravenously and the time of recovery of adequate ventilation again noted. In 12 cases these intervals without tensilon were measured (without giving edrophonium) after the termination of the operation.

It was found that the time for recovery of clinically adequate respiration was significantly reduced by giving edrophonium. As the postoperative observations suggested that the results were not influenced by surgical stimuli the authors administered edrophonium to 30 patients who were either apnoeic or had grossly depressed respiration after operation; of these, 19 showed marked improvement and only one was made worse.

Mark Swerdlow

1484. **Thiopentone Anaesthesia Terminated by Bemegride**

T. E. WAINE and P. DINMORE. *Anaesthesia* [*Anaesthesia*] **13**, 324–328, July, 1958. 7 refs.

An investigation of the antibarbiturate activity of bemegride was carried out at hospitals of the Coventry and Warwickshire Group on patients undergoing dilatation and curettage. Anaesthesia was induced with a sleep dose, followed by minimal supplementary doses, of thiopentone, and bemegride was given intravenously at the end of the operation. The criterion of arousal adopted was opening of the eyes on command. The average duration of operation was 15 minutes and the average dose of thiopentone was 0·5 g. In a preliminary series of 75 cases it was found that the proportion of patients aroused promptly by bemegride varied with the type and amount of premedication. Accordingly a further series of 75 patients received standard premedication with $\frac{1}{6}$ grain (11 mg.) of "omnopon" and $\frac{1}{300}$ grain (0·22 mg.) of scopolamine and only alternate patients received 1 mg. of bemegride per 5 mg. thiopentone after the operation. It was found that the patients who received bemegride awoke significantly sooner than the others. In a further series of 26 patients it was found that a dose of 2 mg. of bemegride per 5 mg. thiopentone (maximum 200 mg. bemegride) produced a higher proportion of successful arousals. Toxic reactions to bemegride were usually of a minor nature, but in one case Jacksonian convulsions occurred 115 minutes after the administration of 280 mg. of the drug. *Mark Swerdlow*

1485. **A Comparison of Barbiturate Antagonists in Thiopentone Anaesthesia**

E. F. O'RIORDAN and A. D. BREWARD. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **37**, 126–129, May–June, 1958. 21 refs.

An investigation of the comparative efficacy of various analeptic drugs was carried out at a British military hospital in Germany on 55 patients undergoing minor operations under thiopentone anaesthesia. At the end of the surgical procedure the patient received an intravenous injection of one of the following: nikethamide, 1 g.; picrotoxin, 6 mg.; bemegride, 50 mg.+daptazole, 15 mg.; and bemegride, 100 mg. Ten subjects who received no analeptic served as controls. Pulse rate, blood pressure, and respiration rate were recorded before and after the administration of thiopentone and after the administration of the analeptic, and note was taken of the time elapsing after the injection of thiopentone before the patient was able (1) to answer his name, (2) to give his Army number, and (3) to leave the hospital.

Although the number of cases studied was too small, as the authors admit, to allow significant conclusions to be drawn, the clinical impression was obtained that bemegride, with or without daptazole, is the most effective means of reversing thiopentone anaesthesia. Picrotoxin produced little acceleration of recovery from anaesthesia. *Mark Swerdlow*

1486. **Cyclopropane in Non-explosive Mixture for Out-patient Anaesthesia**

W. W. MUSHIN and P. W. THOMPSON. *British Medical Journal* [*Brit. med. J.*] **1**, 1376–1378, June 14, 1958. 3 figs., 26 refs.

The authors review some of the literature on the benefits of cyclopropane and the dangers of nitrous oxide in anaesthesia for out-patients, and point out that in regard to cyclopropane the danger of explosion—its most serious disadvantage—can be removed by its admixture with inert gases such as nitrogen or helium. They then report, from the Royal Infirmary, Cardiff, their experience with the use of Hingson's "Western Reserve portable anaesthesia machine" for out-patient anaesthesia in 100 cases.

This apparatus consists of a face-mask provided with a spring valve the purpose of which is to contain the gases within the apparatus until it is applied to the face, a small transparent canister holding 60 g. of soda lime, two midget cylinders of which one contains oxygen and helium and the other cyclopropane and helium, and a 6-litre capacity reservoir bag. Tightening of the aluminium covers placed over the cylinders causes the latter to be perforated by a hollow metal pin through which their contents are then liberated into the reservoir bag to give a mixture of 30% oxygen, 30% helium, and 40% cyclopropane.

On application of the mask to the face consciousness was lost in 15 to 30 seconds and surgical anaesthesia achieved in 45 to 90 seconds. In a few cases transient coughing or breath-holding occurred before surgical anaesthesia was produced, but only 2 of the patients struggled for a brief period and no case of apnoea occurred. It was found that inhalation for 2 to 3 minutes produced at least one minute of perfect surgical anaesthesia after removal of the mask, while this period could be prolonged by the nasal administration of nitrous oxide and oxygen, particularly in dental cases. Bleeding and salivation were sometimes more marked than with nitrous-oxide–oxygen anaesthesia, and the use of suction apparatus is recommended in such cases. No cyanosis due to exhaustion of oxygen was observed. The value of the small soda-lime canister was demonstrated by a laboratory investigation which showed that the concentration of carbon dioxide in the bag rose to 1% at the end of 2 minutes and to 1·75% at the end of 5 minutes, whereas in a study on volunteer subjects in which the soda-lime canister was omitted the carbon dioxide concentration in the bag rose to 7% at the end of 2 minutes.

Recovery from anaesthesia occurred within 1 to 1½ minutes in most cases, but drowsiness and giddiness often persisted for up to 10 minutes and 10% of the patients vomited in the immediate post-anaesthetic period; although the vomiting was very slight it was more frequent than with nitrous oxide and oxygen. The authors end by emphasizing that the certainty that the mixture here described is not flammable or explosive lies in the use of the special cylinders supplied with the apparatus. They " strongly discourage any attempt to make a non-inflammable mixture of cyclopropane for routine clinical use by drawing it from a cylinder of pure gas ". The method carries no higher morbidity or mortality than the method it is recommended to replace.

Raymond Vale

1487. **Cyclopropane Anesthesia. I. Cardiac Rate and Rhythm during Steady Levels of Cyclopropane Anesthesia at Normal and Elevated End-expiratory Carbon Dioxide Tensions**

A. A. Lurie, R. E. Jones, H. W. Linde, M. L. Price, R. D. Dripps, and H. L. Price. *Anesthesiology* [*Anesthesiology*] **19**, 457–472, July–Aug., 1958. 3 figs., 15 refs.

Continuous-record studies were made at the University of Pennsylvania School of Medicine, Philadelphia, to determine the significance of the cardiac arrhythmias which may occur during cyclopropane anaesthesia. The 31 patients investigated were anaesthetized without premedication, and no other drug than cyclopropane was used, except heparin to keep the intra-arterial needle patent. A 20-minute period of oxygen breathing was given, followed by induction and intubation. Various arrhythmias occurred, in the absence of hypercarbia, in 19 out of 29 subjects, their incidence increasing with the depth of anaesthesia. They occurred more frequently and for longer periods during hypercapnia, in the presence of which ventricular arrhythmias may occur at any cyclopropane concentration in the anaesthetic range. An increase in systolic pressure preceded the onset of arrhythmia. Excessive secretions were present during anaesthesia, and this was considered to be due to the absence of premedication. There was a high incidence of nausea, vomiting, and emergence excitement. Details of methods of monitoring are given.

It is concluded that cyclopropane can initiate ventricular arrhythmias in man under normal conditions. Their incidence rises with the concentration of the gas, and they invariably occur if hypercapnia is allowed to develop. A rapid return from hypercapnia towards normal also initiates or aggravates them. The fact that they can generally be prevented or abolished by spinal anaesthesia suggests that they may originate in the sympathetic nervous system. They do not appear to be deleterious.

W. Stanley Sykes

1488. **Anesthetic, Circulatory and Respiratory Effects of Fluothane**

T. K. Burnap, S. J. Galla, and L. D. Vandam. *Anesthesiology* [*Anesthesiology*] **19**, 307–320, May–June, 1958. 3 figs., 14 refs.

At the Peter Bent Brigham Hospital, Boston, halothane (" fluothane ") was employed as the anaesthetic agent for 102 unselected patients aged from 10 to over 80 years undergoing a wide variety of operations, electrocardiographic, electroencephalographic (EEG), and other data being recorded during the anaesthesia. Liver function tests, and in some cases liver biopsies, were also performed. After minimal premedication anaesthesia was induced by both closed and semi-closed methods, using Heidbrink and Foregger vaporizing machines. Induction was smooth and emergence tranquil, the incidence of nausea and vomiting being similar to that seen after other general anaesthetics. Intubation was carried out in 63 cases, in 41 without the use of relaxants. Arrhythmias sometimes occurred after intubation, most frequently when halothane alone was used. Signs of the depth of anaesthesia were deceptive; any degree of pupillary dilatation indicated good relaxation, but was always accompanied by profound hypotension. Tachypnoea and depression of tidal volume sufficient to require controlled respiration were consistently present. The EEG was of little help in indicating the depth of anaesthesia.

Halothane is a potent depressor of the cardiovascular system, especially in a closed system, and moderate to severe hypotension developed in 54 of the 102 cases. Vasopressor drugs controlled this effect in most instances, but halothane had to be discontinued in 3. Pre-existing cardiac arrhythmias were not increased in severity. In addition to rapid and very shallow breathing, carbon

dioxide retention occurred. Liver function studies in 2 of 7 cases showed a worsening of liver disease; that this was attributable to the effects of halothane could not be determined with any certainty. The authors suggest, however, that it may be better to avoid this drug when previous liver damage exists. Because of the potency of halothane the signs of anaesthesia induced with it are not easy to interpret either clinically or with EEG control. In the authors' experience accurate vaporizers are essential and the closed circuit should be avoided. The great advantage of halothane, of course, is its non-inflammability. *W. Stanley Sykes*

1489. **Observations during Experimental and Clinical Use of Fluothane**

R. W. Virtue, K. W. Payne, L. J. Caranna, G. S. Gordon, and R. R. Rember. *Anesthesiology* [*Anesthesiology*] **19**, 478–487, July–Aug., 1958. 23 refs.

Experiments were carried out at the University of Colorado, Denver, in an attempt to answer the question whether "fluothane" (halothane) sensitizes the heart to adrenaline as chloroform is known to do. Dogs were anaesthetized with fluothane or with chloroform and ether and the results compared. "Bromsulphalein" retention following ether anaesthesia was almost identical with that after fluothane anaesthesia, but chloroform produced greater retention. Of 4 dogs receiving adrenaline during fluothane anaesthesia, 2 developed ventricular fibrillation and a third had ventricular tachycardia. Fluothane did not affect the liver as did chloroform.

The animal experiments were followed by observations on 12 patients undergoing various surgical procedures. It was found that the blood glucose level was increased during an hour of fluothane anaesthesia, but returned to normal by next morning. The results of other laboratory investigations were little different from preoperative findings. Induction was easy with a 2% concentration of the drug, and hypotension was produced by mild overdosage; relaxation was good and recovery rapid. Fluothane is an extremely potent agent, and not considered safe unless an apparatus for producing controlled low concentrations is used. Standard machines could not be calibrated to deliver safe and consistent concentrations. *W. Stanley Sykes*

1490. **Evaluation of Inhalers for Trichloroethylene, Chloroform and Fluothane**

S. H. Ngai, H. D. Green, J. R. Knox, and H. C. Slocum. *Anesthesiology* [*Anesthesiology*] **19**, 488–500, July–Aug., 1958. 6 figs., 8 refs.

On the assumption that in the event of mass casualties relief of pain would have to be produced by self-administered analgesia or at the hands of unskilled personnel a study was made at the Walter Reed Army Medical Center, Washington, D.C., to explore the analgesic properties of non-inflammable inhalation drugs and to discover methods of their safe administration under such conditions. The drugs tested were trichloroethylene, chloroform, and "fluothane" (halothane). Six inhalers were evaluated, each with one, two, or all three of the agents under trial, concentrations of anaesthetic mixtures being analysed by infra-red spectrophotometry. The authors' findings were as follows.

(1) The Duke inhaler delivered chloroform vapour in a concentration of up to 2·12%, which is too high for analgesic purposes. It is light and compact, and performs well with trichloroethylene. (2) The Duke inhaler modified by fixing a metal cap with various-sized openings and adjusting the outlet port to reduce the air flow delivered a maximum concentration of 1·66%, thus making it suitable for use with chloroform. (3) The "emotril" inhaler did not give stable concentrations until after 15 to 30 minutes' use. It has a thermo-compensating mechanism. (4) The "tecota" inhaler Mark VI, which is designed for trichloroethylene, has a thermo-compensating mechanism and stabilizes rapidly. (5) With the "airlene" inhaler variations in tidal volume and altered positions of the apparatus altered the concentrations in an irregular manner. (6) An experimental tecota inhaler calibrated for use with chloroform gave a stable concentration at 0·8% or lower, but at 1·0% or above the concentration fell rapidly. Variations in minute volume did not significantly alter the concentration, and in this respect this inhaler appears to be superior to the others tested. It has a thermo-compensating mechanism.

The modified Duke inhaler, the tecota Mark VI, and the experimental tecota inhaler were used in a study of chloroform analgesia in experimental animals and in man and found to give a satisfactory performance. The authors consider, however, that further studies are needed as to the desirability of using chloroform and fluothane for analgesia in the circumstances envisaged in the present investigation. *W. Stanley Sykes*

1491. **Levallorphan. Effects of Large Doses**

M. Swerdlow. *Anaesthesia* [*Anaesthesia*] **13**, 318–323, July, 1958. 5 refs.

Levallorphan has been shown to be an effective antagonist of many of the effects of the narcotic analgesics. In an attempt to discover possible ill effects of the drug the author, working at Salford Royal Hospital, Manchester, administered levallorphan in increasing doses to patients under various conditions.

In 6 conscious, unpremedicated patients doses of 7 to 10 mg. of levallorphan given intravenously caused transient sensations of vertigo, paraesthesiae, drowsiness, and heaviness. There was little change in the respiratory rate, but the minute volume was reduced, in 2 cases markedly. In 6 conscious patients given premedication with morphine (11 mg.) and atropine (0.64 mg.) the intravenous injection of 5 to 10 mg. of levallorphan caused minimal changes in the respiration rate, but a moderate reduction in the minute volume. Finally, in 6 patients premedicated with morphine and atropine and anaesthetized with thiopentone–nitrous-oxide–oxygen–halothane or with thiopentone–nitrous-oxide–oxygen the intravenous injection of 5 to 7 mg. of the antagonist produced only small changes in the respiratory rate and volume.

The doses of levallorphan given were many times larger than those recommended for clinical use, and the findings suggest that this drug has a high margin of safety when used as an antidote to the opiates.—[Author's abstract.]

Radiology

1492. **Expectation of Life and Mortality from Cancer among British Radiologists**

W. M. COURT BROWN and R. DOLL. *British Medical Journal* [*Brit. med. J.*] **2**, 181–187, July 26, 1958. 20 refs.

It has been reported by the U.S. National Academy of Sciences that the average age at death of American radiologists is about 5 years lower than that of American physicians who have no occupational exposure to radiation, it being inferred that, just as the longevity of animals subjected experimentally to whole-body irradiation in large doses is reduced, repeated exposure to radiation as experienced by radiologists produces a similar decrease in expectation of life. On the other hand it has been claimed that exposure even to small doses of radiation results in some impairment of the ability to survive, and accumulated genetic damage to the somatic tissues, resulting in an increased rate of ageing, has been offered as an explanation of such a non-specific effect. The objects of the present investigation were (1) to see whether there was evidence for a decrease in the expectation of life due to a non-specific ageing effect among British radiologists, and (2) to examine their mortality from cancer.

The population studied consisted of all medical and dental members, up to the end of 1954, of the British Institute of Radiology and the Faculty of Radiologists and their precursors, the lists compiled from the records of these bodies being retrospective to 1897 and 1934 respectively. Of a total of 2,035 members, 1,461 had an initial address in Great Britain or Ireland or were members of the Colonial or Armed Services and were regarded as constituting the " home " population. For simplicity of analysis women were excluded and the study limited to the 1,381 men in the " home " population. The authors point out that no data exist which would permit reasonable assessments to be made of the total exposure to radiation of individuals, but they argue that the population can reasonably be divided into two groups on the basis of likely exposure. It was assumed that men joining the societies after 1921 would largely be practising under recognized conditions of protection resulting from the recommendations of the British *X*-ray and Radium Protection Committee, whereas the degree of exposure experienced by those joining before that date would, on the whole, have been excessively high. For each of these two groups the number of man-years of exposure to risk was calculated by age groups and chronological periods and the results are tabulated. For comparison with the number of deaths observed in each exposure group and each chronological period calculations were made of the number of deaths expected on the basis of three different hypotheses—namely, that the observed age-specific mortality from all causes was the same as that of (1) all men in England and Wales, (2) all men in Social Class I, and (3) all doctors, at the relevant time. Some reasonable adjustments were made to the crude data available from the Registrar-General's reports for calculating the expectations, and further corrections were made to the expectations from the last two hypotheses in order to counteract the bias in published occupational and social-class mortality at ages over 65 years. Similar observations and expectations are tabulated for deaths attributed to cancer of all and various sites.

In all chronological periods combined there were 302 deaths from all causes in the pre-1921 group and 161 in the post-1921 group. On the basis of the first hypothesis the expected numbers were 324 and 201 respectively; on the basis of the second hypothesis they were 306 and 193 respectively after correction for " age bias " and 322 and 200 before such correction; and on the basis of the third hypothesis the expected numbers were 322 and 192 respectively after correction and 322 and 193 respectively before correction. Further comparisons between observed and expected numbers for various chronological perjods gave no evidence in support of a non-specific shortening of life expectancy. In total, 463 deaths were observed, and this is considerably less than the number expected on the basis of any of the hypotheses, the minimum expectation being 499.

A similar examination of the mortality from cancer showed that among radiologists in the post-1921 group there were 24 deaths from this cause, the smallest number expected being 26 on the basis of the third hypothesis after correction for " age bias ". However, among radiologists in the pre-1921 group a significant excess of deaths from cancer was observed, the number of deaths observed being 55, whereas the highest expected number, based on the first hypothesis, was 48 and the lowest, based on the third hypothesis after correction for " age bias ", was 25. More detailed examination showed that this excess was confined to tumours of the skin (6 cases observed) and pancreas (6 cases observed) and possibly leukaemia (2 cases observed); for these conditions the observed mortality was 4 to 6 times greater than that expected from the experience in the general population.

E. A. Cheeseman

1493. **Strontium in Diet**

F. J. BRYANT, A. C. CHAMBERLAIN, G. S. SPICER, and M. S. W. WEBB. *British Medical Journal* [*Brit. med. J.*] **1**, 1371–1375, June 14, 1958. 2 figs., 12 refs.

The authors report, from the Atomic Energy Research Establishment, Harwell, Berks, the results of an investigation carried out during 1957 of the stable strontium and radioactive strontium (^{90}Sr) content of the principal items of diet. Most of the samples were taken in Wales and in the west and north of England, since these are the regions of highest rainfall and therefore of the highest " fall-out " of radioactive material. The findings, presented in a series of tables in an appendix, include those for flour, vegetables, dried milk, liquid milk from hill farms, and for animal bones and other products. No estimations were made on meat, but on certain

assumptions it is considered that the ratio of strontium in the flesh of an animal will be similar to that in its bones.

The mean ^{90}Sr:calcium ratio in the adult diet in the summer of 1957 was 5·6 $\mu\mu$c.:g., which is about the same as the ratio in the milk portion of the diet alone. Individuals who draw their milk and other food supplies from farms in an area of high rainfall and with an acid or calcium-deficient soil may have a significantly higher ratio of ^{90}Sr:Ca in their diets, but the extreme variation is unlikely to exceed a factor of 5. The mean ratio of stable strontium to calcium in the diet was 1,200 μg.:g., that is, about four times the ratio in the milk portion alone. The authors conclude as follows: " There appears to be a discrimination of about 4:1 against strontium in favour of calcium in uptake from food to human bone. The strontium-90 : calcium ratio (S. U.) [$\mu\mu$c. of ^{90}Sr per g. of calcium] in newly laid down bone is deduced to be between 1 and 2 S.U. for individuals on mixed diet."

L. A. Elson

1494. **Effect of Temperature on the Course of Radiation Sickness.** (К вопросу о влиянии окружающей температуры на течение лучевой болезни)
L. N. Mušina-Udgodskaja. *Вестник Рентгенологии и Радиологии* [*Vestn. Rentgenol. Radiol.*] **33**, 23–27, No. 3, May–June, 1958. 9 refs.

When acute radiation sickness was experimentally induced in white rats it was found that its severity depended to a considerable extent on the temperature at which the animals were kept. The mortality from radiation sickness was 95% in animals kept at a temperature of 20° to 25° C., while among animals kept at a temperature of 8° to 10° C. the mortality from the same dose of radiation was only 5%. The effect of environmental temperature was most marked on mortality, though the clinical manifestations, the morphological changes in various organs, and the blood picture were also affected, but to a lesser degree.

A. Orley

1495. **Mechanism of Emesis following *X*-irradiation**
S. C. Wang, A. A. Renzi, and H. I. Chinn. *American Journal of Physiology* [*Amer. J. Physiol.*] **193**, 335–339, May, 1958. 6 refs.

The authors have previously reported that whereas dogs exposed to 800 r. total body irradiation vomited within 2 hours, this immediate effect was abolished by destruction (even if incomplete) of the chemoceptive emetic trigger zone in the medulla, though it was observed that dogs so treated began to vomit after a few days and continued to do so throughout their survival period. In further experiments reported here it was found that visceral deafferentation alone (abdominal vagotomy and sympathectomy) did not prevent dogs from vomiting soon after irradiation. But both early and delayed vomiting were abolished by combining the two procedures.

It is therefore concluded that the vomiting of radiation sickness is mediated through two mechanisms—the central trigger zone and the peripheral visceral afferent receptors of the vagal and sympathetic trunks. For the early emetic effect of irradiation the chemoceptive trigger zone is alone responsible, though the chemical mediator, which must be some circulating substance liberated in the tissue reaction, is unknown. A direct effect of radiation on the medulla is unlikely, since very high local doses rarely cause vomiting. The delayed effect, which occurs even after complete destruction of the central zone, but cannot be abolished by visceral deafferentation alone, appears to be the result of either central or peripheral stimulation. The mechanism of stimulation of the gastro-intestinal receptors is unknown, though since intestinal mucosal erosions and petechiae were almost always found at necropsy in the authors' animals it is possible that this condition is the cause of the local irritation.

J. Walter

RADIODIAGNOSIS

1496. **The Peripheral Pattern in the Normal Bronchogram and Its Relation to Peripheral Pulmonary Anatomy**
L. Reid and G. Simon. *Thorax* [*Thorax*] **13**, 103–109, June, 1958. 10 figs., 10 refs.

Although the radiological appearances of the main bronchial subdivisions have frequently been described, the detailed structure of the smaller peripheral bronchi and the associated pulmonary structure have not received the same attention. The present authors, at the Institute of Diseases of the Chest and Brompton Hospital, London, have accordingly scrutinized a large number of normal bronchograms with particular reference to the bronchial pattern at the lung edge. This has been supplemented by a study of normal lungs taken from cadavers and injected with a contrast material. Radiographs were taken of these lungs and sections then cut from identifiable regions and examined serially under low magnification.

A constant type of pattern in the bronchiole structure was observed. Beyond the half-way point from the lung centre the bronchi assumed the form of fine lines having parallel edges. These branched at 0·5- to 1·0-cm. intervals, a type of branching to which the authors give the term the " centimetre pattern ". These branchings terminated in fine lines in which side branches were given off at about 2-mm. intervals; these branches were short and opened into the acinar structure of the lung. This type is termed the " millimetre pattern ".

In the normal bronchogram the acini and alveoli seldom fill. " Woolly " peripheral shadows, which many observers have attributed to alveolar filling, are shown by a lateral view to result from superimposed " millimetre " branchings.

A. M. Rackow

1497. **The Secondary Lobule in the Adult Human Lung, with Special Reference to Its Appearance in Bronchograms**
L. Reid. *Thorax* [*Thorax*] **13**, 110–115, June, 1958. 3 figs., 15 refs.

The primary lobule of the lung has been defined as that part embracing the respiratory elements at the end of the terminal bronchiole, and this includes acini, atria, and alveoli. In attempting to define the limits of the secondary lobule the author found two of the existing criteria to be unsatisfactory. The first of these, which defines the

secondary lobule by the presence of septa, fails because these septa are found to be very irregular in extent and distribution. The other, which defines the lobule as that part of the lung lying beyond the cessation of cartilage in the bronchus, is also invalid, since examination of these terminal bronchi shows that the cartilage ceases at a very variable distance from the lung periphery.

Examination of a large number of normal bronchograms, lung specimens, and sections both injected and uninjected, showed that the site at which the smaller bronchioles assumed the "millimetre pattern" of branching—that is, where terminal bronchioles arose at about 2-mm. intervals—formed a very suitable definition of a secondary lobe. The cluster of terminal bronchioles, usually 3 to 5 in number, was associated with a volume of respiratory tissue of about 1 to 2 c.cm. This formed a unit which was large enough to be perceptible on clinical bronchography as well as on macroscopical and microscopical examination. *A. M. Rackow*

1498. **Pneumocisternographic Exploration of the Posterior Fossa.** [In English]
A. MORELLO. *Acta neurochirurgica* [*Acta neurochir. (Wien)*] **6**, 81–92, 1958. 7 figs., 24 refs.

For the investigation of lesions of the posterior fossa the author has developed a technique in which the posterior fossa, the 4th ventricle, and the aqueduct are filled with air injected by the lumbar route. The method consists in lumbar injection of 30 ml. of air (12 to 25 ml. in children and in cases of increased intracranial pressure) with the patient lying on his side on a tilting table. At the end of the injection the head of the table is lowered to 5 degrees below the horizontal and the patient turned into the prone position. The head is placed so that the orbito-meatal line is perpendicular to the plane of the table, the latter then being raised so that the head is 30 degrees above the horizontal. A total of 7 radiographs (5 lateral and 2 postero-anterior) are taken, the head being dorsiflexed between the earlier and later exposures. This method gives good visualization of the cisterna magna and the pontine, interpeduncular, and ambiens cisterns, together with the 4th ventricle, aqueduct, and the posterior part of the 3rd ventricle. The author claims that the method may be used even in cases of raised intracranial pressure without deleterious effect, pressure coning being less liable to occur than during lumbar encephalography in the sitting position. The importance of visualizing the subarachnoid cisterns in patients with lesions of the posterior fossa is stressed. Six illustrative cases are described. *J. B. Stanton*

1499. **The Radiological Diagnosis of Congenital Duodenal Atresia in the Newborn.** (Рентгенодиагностика врожденной дуоденальной непроходимости у детей грудного возраста)
G. B. FOMIN. *Педиатрия* [*Pediatrija*] **36**, 50–55, No. 5, May, 1958. 4 figs., 9 refs.

Congenital narrowing of the duodenum, though rare, is not so uncommon as has been believed, for some 160 cases have been described (15 in the U.S.S.R.), apart from the 9 on which the present observations are based. The symptoms resemble those of pyloric stenosis, but vomiting is neither so pronounced nor so forcible. The presence or absence of bile in the vomitus depends upon the site of the atresia. The diagnosis can be made on the radiographic appearances, which are of two types: in one, the duodenum is uniformly dilated as far as the obstruction, but its shape is unchanged, whereas in the other the duodenal shadow resembles a mirror-image of the stomach, with a three-layer content (barium below, then intestinal fluid, and on top a gas-bubble). The plain radiograph of the abdomen shows a horizontal level of fluid, with a gas-bubble under the liver shadow. Any delay in the clearance of barium from the duodenum is suggestive of obstruction, since normally its passage through this part of the intestine is rapid. Hence radiology offers a means of accurate and quick diagnosis and enables surgical treatment to be undertaken at an early stage, which is essential if the infant's life is to be saved. *L. Firman-Edwards*

1500. **A Clinical Evaluation of Nephrotomography**
W. F. W. SOUTHWOOD and V. F. MARSHALL. *British Journal of Urology* [*Brit. J. Urol.*] **30**, 127–141, June, 1958.

The authors, who write from the New York Hospital and Cornell University Medical College, New York, have aimed at evaluating nephrotomography from a clinician's point of view. Their technique is as follows. A preliminary plain film and tomograms are made. A Robb–Steinberg angiocardiographic needle is then inserted percutaneously into an arm vein. The arm-to-tongue circulation time is measured by rapid intravenous injection of 5 ml. of 20% "decholin" (dehydrocholic acid) and timing the appearance of a bitter taste; most recently 25 ml. of 50% "hypaque" (sodium diatrizoate) has also been injected. Following this is 50 ml. of 90% hypaque, injected with a further 5 ml. of decholin, the injection being performed in less than 2 seconds. The first plain film is exposed one second after the patient experiences a bitter taste or one second after the arm-to-tongue circulation time, whichever is the shorter. A second plain film is exposed 3 to 4 seconds later. Immediately after this exposure 3 or 4 tomographic films are made at predetermined levels, usually 9, 10, 11 and 12 cm. The examination is repeated if the results on the first occasion prove unsatisfactory. After a few minutes ordinary pyelographic films are made. In general, in the "arteriographic phase" (first film) a cyst shows as an almost avascular area circular in outline, while a tumour appears as an irregular blotchy opacification. In the nephrogram (second film) a cyst appears as a radiotranslucent area surrounded by evenly opacified parenchyma except for the common finding of a 1- to 2-mm. halo of increased density, while a tumour appears as an irregular blotchy opacification. The tomogram largely obliterates the obscuring effects of overlying gas shadows. The authors are of the opinion that masses greater than 2 cm. in diameter can nearly always be visualized by this technique, whereas if they measure 1 cm. or less they will be difficult to evaluate.

Of the first 272 cases examined, 20 were technically too inadequate for a diagnosis to be made. The nephrogram

in 93 cases was considered to show normal kidneys. Only 4 of these interpretations are known to be in error, in one case a superficial cyst, in 2 a carcinoma, and in one multiple cysts being found at operation. No long-term follow-up has yet been possible, and therefore the authors withhold a final judgment as to the value of the method in excluding renal disease. In 115 cases a diagnosis of non-neoplastic cyst was made, this being regarded as proved by operation or aspiration in 80 cases. Five of the cases were misdiagnosed, 3 proving to be cases of carcinoma, one of chronic nephritis and one of foetal lobulation; in 3 of these 5 cases the films were regarded as unsatisfactory.

Of the 44 remaining cases, in which a neoplasm was diagnosed, in 41 this diagnosis has been proved correct while 2 were found to have a cyst and one chronic pyelonephritis only. *John H. L. Conway-Hughes*

RADIOTHERAPY

1501. **Results of Close-range Irradiation of Carcinoma of the Eyelid.** (Ergebnisse der Nahbestrahlung von Lidkarzinomen)
W. MOLDENHAUER. *Klinische Monatsblätter für Augenheilkunde* [*Klin. Mbl. Augenheilk.*] **132**, 335–350, March, 1958. 8 figs., bibliography.

There is no treatment of choice for carcinoma of the eyelid. Good results may be obtained by operation or close-range irradiation. Functional and cosmetic results are often better after irradiation. Extensive carcinomata should be treated by the ophthalmologist and radiologist together. In a series of 117 cases of carcinoma of the eyelid treated with close-range irradiation 96.6% showed freedom from symptoms and 87·6% relative cure. Recurrences are more difficult to treat. A recurrence after *x*-irradiation may be treated again by irradiation provided the exposure has been moderate; otherwise it should be treated operatively because of an increased resistance to irradiation. Prophylactic close-range irradiation is not favoured. Biopsy should not be carried out if the diagnosis is not in doubt. The cause of 8 recurrences was assumed to be too small a field of exposure and too little penetration. The Müller-RT-50 close-range irradiation apparatus with its short exposure seems, for technical reasons, suitable for the treatment of carcinoma.—[From the author's summary.]

1502. **Lesions of the Salivary Glands**
D. G. MCEACHEN, D. F. MOORE, E. M. NANSON, and T. A. WATSON. *Surgery, Gynecology and Obstetrics* [*Surg. Gynec. Obstet.*] **106**, 655–666, June, 1958. 16 refs.

The authors discuss lesions of the salivary glands, especially the parotid gland where the chief pathological condition is tumour formation and surgery is difficult because of the proximity of the facial nerve. Of 155 salivary-gland lesions seen at the Cancer Clinic, Saskatoon, Saskatchewan, between 1932 and 1956, 129 were neoplasms and 26 were miscellaneous lesions. Of the 129 neoplasms, 85 were benign and 44 malignant, the former including 72 mixed salivary tumours, 6 adenolymphomata, and 7 tumours at other sites. The authors state that adenolymphomata do not recur when completely excised. Benign mixed tumours may recur at any time; in one reported series there was recurrence 47 years after the first treatment, but usually the interval is about 5 years. They are pleomorphic adenomata and are more common in females than in males.

Of 79 benign mixed tumours, 62 were primary and untreated and 17 were recurrent growths. In 50 of the 62 cases of primary tumour irradiation was carried out, combined with surgery in 49; in the remaining 12 treatment was by surgery alone. The over-all recurrence rate in cases of benign mixed salivary tumour was low—namely, 6%. From these findings the authors draw the following conclusions: (1) a long period of follow-up—at least 20 years—is necessary in cases of mixed salivary tumour; (2) local surgery and postoperative irradiation give excellent results without sequelae; (3) irradiation alone can be curative; (4) local surgery in untreated cases can be successful; and (5) local surgery alone is not satisfactory in the treatment of recurrence.

Of the 44 malignant salivary tumours in the series, 17 were mixed and 27 were carcinomata. Treatment was by surgery alone, irradiation alone, or a combination of these. The over-all 5-year survival rate in the whole group of 44 cases was 65%, but in the 24 previously untreated cases it was 71%. The authors consider from these results that in the treatment of malignant salivary-gland tumours a combination of surgery (even local) and postoperative irradiation is successful in a high percentage of cases; irradiation alone can be effective in eradicating the disease, but surgery of a local type by itself is unlikely to be successful.

Finally, the need for adequate planning of the treatment and management of salivary-gland tumours is emphasized. Surgery should be adequate and irradiation should be used as an adjunct to surgery. Parotid-gland tumours " are series lesions, one-third are malignant, and are deceptively easy to remove. They should not be treated lightly ".

[This excellent paper should be read in the original by those interested.] *R. D. S. Rhys-Lewis*

1503. **Radiotherapy for Malignant Tumours of the Thyroid**
G. W. BLOMFIELD, *Proceedings of the Royal Society of Medicine* [*Proc. roy. Soc. Med.*] **51**, 522–525, July, 1958. 2 refs.

The author reviews 100 consecutive cases of thyroid carcinoma referred to the Sheffield National Centre for Radiotherapy during the 9 years 1946–55. The symptomatology and pathology are discussed. Of the 83 patients whose survival for 5 years was possible, 34 actually survived that period without recurrence—a rate of 41%, compared with 18, or 69%, of the 26 with papillary-type carcinoma. Metastases were found at some time during the course of the disease in 59% of the patients, and, as pointed out, this figure is necessarily incomplete. Treatment by surgery combined with deep *x* rays was relatively successful, 52% of the patients treated by this method surviving 5 years. Deep *x*-ray

therapy alone yielded a 5-year survival rate of only 18%, but the cases given this treatment were mostly of high malignancy.

Technical difficulties are discussed and the superiority of supervoltage *x* rays is stressed. Only 7 of the 100 cases appeared suitable for radioactive iodine therapy, and in one patient, a girl of 17 with recurrent metastases in the neck, complete regression which has lasted 8 years was obtained with a dose of 67 millicuries. The author emphasizes that mere bulk of the tumour may make it impossible to give a sufficiently large dose of radioactive iodine. *E. Stanley Lee*

1504. **Endobronchial Irradiation of Carcinoma of the Bronchus.** (Die endobronchiale Bestrahlung des Bronchuskarzinoms)
H. J. BRANDT and W. SCHLUNGBAUM. *Strahlentherapie* [*Strahlentherapie*] **105**, 207–217, 1958. 6 figs., 10 refs.

A method of using radioactive cobalt (^{60}Co) intrabronchially for the treatment of carcinoma is described from the Free University of Berlin. The ^{60}Co is contained in beads threaded on a string. Under general anaesthesia, and with the help of a specially designed bronchoscope, the beads are placed in apposition with the bronchial neoplasm for periods lasting up to 4 hours, giving a surface dose to the tumour of 4,000 r. The patient remains anaesthetized and respiration is controlled throughout the period of application. In some cases the treatment was repeated after an interval of at least 7 days.

The method, which is employed only in advanced cases or those unsuitable for external irradiation, is said to be particularly indicated in patients with endobronchial tumours causing obstruction of major branches of the bronchial tree. Five illustrative case histories are presented. *Jan G. de Winter*

1505. **The Treatment of Lung Cancer (Primary and Metastatic) by Radioactive Phosphorus Administered Intravenously, Intra-arterially and Intracardially**
I. M. ARIEL. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **79**, 961–980, June, 1958. 11 refs.

At the Pack Medical Foundation, New York, the palliative treatment of both inoperable primary cancer of the lung and metastatic lung cancer was attempted by intravenous injection of radioactive phosphorus (^{32}P). The dosage varied between extremes of 4 mc. and 20·5 mc.; the average dose was 10 mc. given in two doses of 5 mc. each with an interval of a week between. Altogether 51 patients were treated; no serious reactions occurred, and the haematopoietic depression was slight or absent.

The percentage pick-up by primary lung tumours at half an hour after injection of ^{32}P varied between 14 and 117, with an average of 40 in the 8 patients in whom this was measured. Roughly similar figures were obtained in 30 cases of pulmonary metastases from cancer of breast, female genitalia, colon, or rectum, and a miscellaneous group of sarcomata. The notable feature was the great variation in pick-up, which could not be correlated with tumour type, size, or location. In the hope of obtaining greater concentration of radioactivity in the tumour the ^{32}P was injected directly into the right auricle of one patient through a polythene tube in the brachial vein and in 4 others it was injected into the thoracic aorta through a catheter in the femoral artery. None of these patients showed a significantly greater concentration of ^{32}P in the tumour compared with patients given the isotope intravenously. In 9 cases a course of nitrogen mustard (mustine) was given after the injection of ^{32}P, followed in about a week by a second injection of ^{32}P; however, this did not appear to enhance pick-up; indeed in several cases less pick-up was observed after the nitrogen mustard had been given.

The author states that although prolongation of life was not observed, troublesome symptoms such as cough, pain, and to a less extent dyspnoea, were alleviated in a significant proportion of cases, but the relief was usually transient. This alleviation was found only in cases of primary lung cancer and metastatic breast cancer, and was not seen in cases of lung metastases from cancer of female genitalia, colon, and rectum. Objective improvement, such as changes in the *x*-ray appearances, was not observed. *E. Sherrah-Davies*

1506. **Interstitial Implantation in the Treatment of Primary Bronchogenic Carcinoma**
U. K. HENSCHKE. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **79**, 981–987, June, 1958. 3 figs., 11 refs.

In the treatment of bronchogenic carcinoma at the Memorial Center for Cancer and Allied Diseases, New York, interstitial implantation of radioactive material at the time of thoracotomy has been tried, and in this paper the technique and results are described. It is pointed out that in approximately one-third of all cases of primary bronchogenic carcinoma resection is planned, but that in 43% exploration shows that the tumour is too advanced for excision. The author therefore considers that instead of merely performing a thoracotomy and taking a biopsy specimen for examination, interstitial implantation should be carried out in such cases before the chest is closed.

The results obtained with radon seeds in 119 patients seen between 1941 and 1955 are described. One patient only is still living, having survived 5 years, and 3 others survived 53, 35, and 29 months respectively. None of the remainder survived more than 28 months; the average survival period was 10 months. There was no statistical difference between the survival times of patients with epidermoid carcinoma, adenocarcinoma, and anaplastic carcinoma. Since 1956 a new implantation technique has been used, in which unloaded hollow needles are first placed in the tumour and the seeds are inserted into these needles, a special instrument to which a depth gauge is attached being used. A well spaced volume implant is thus achieved; the implant is permanent.

Recently radioactive iridium (^{192}Ir) has been used instead of radon, the reasons for this change being that ^{192}Ir is less expensive than radon, it has a much longer half-life (74 days) making it possible to keep an adequate supply of sources available for future operations, and the

radiation exposure is much lower with ^{192}Ir than with radon. One case is described in which implantation with ^{192}Ir was carried out, 284 sources being used, giving a total activity of 23 mg. radium equivalent. The dose for total decay in the implanted volume was calculated from the Parker–Paterson tables to be 33,500 r. This was the most extensive implant in the series. The question whether such large implants give worthwhile clinical results or whether implants should be reserved for smaller tumour masses must, in the author's view, await further study.

K. S. Holmes

1507. **Radioactive Colloidal Chromic Phosphate to Control Pleural Effusion and Ascites**

M. L. JACOBS. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **166**, 597–599, Feb. 8, 1958. 9 refs.

The author describes the treatment of 41 patients with malignant pleural effusion and 16 with malignant ascites at the City of Hope Medical Center, Duarte, California. A comparison is made between radioactive colloidal gold (^{198}Au) and radioactive chromic phosphate ($Cr^{32}PO_4$) as a source of radiation. $Cr^{32}PO_4$ is considered to be preferable to ^{198}Au for the following reasons: it has no gamma-ray component and is therefore safer for other patients and staff; it has a longer half-life; and the initial dose needed is smaller. However, contaminated linen and equipment need a longer period of isolation for decay. The preparation of $Cr^{32}PO_4$ is outlined and the technique of administration through a polythene tube after paracentesis described. It is hoped by this method to avoid loculation of the isotope with resulting necrosis of the intestine.

Good results are reported in 25 of the 41 cases of malignant pleural effusion and in 5 of the 16 cases of ascites. In all cases there was histological proof of the site and nature of the primary lesion. *R. D. S. Rhys-Lewis*

1508. **The Use of Radioactive Phosphorus in the Therapy of Leukemia, Polycythemia Vera and Lymphomas: a Report of 10 Years' Experience**

R. B. CHODOS and J. F. ROSS. *Annals of Internal Medicine* [*Ann. intern. Med.*] **48**, 956–977, May, 1958. 7 figs., 35 refs.

In this paper from the Massachusetts Memorial Hospitals, Boston, the authors report the results obtained with radioactive phosphorus (^{32}P) over a 10-year period in the treatment of chronic granulocytic leukaemia (30 cases), chronic lymphocytic leukaemia (12 cases), polycythaemia vera (7), multiple myelomatosis (7), Hodgkin's disease (4), acute leukaemia (8), mycosis fungoides (2), and chronic monocytic leukaemia (one case). Many patients in this series [exact number not stated] received other forms of treatment (blood transfusion, wide-field or local irradiation, and drugs including phenylhydrazine and steroids) either before or after administration of ^{32}P; [it is therefore impossible to assess the true value of ^{32}P in this series]. Usually ^{32}P was given intravenously, the dosage varying widely in time and amount. In cases of polycythaemia vera and chronic lymphatic or myelogenous leukaemia ^{32}P was given only when the peripheral blood count showed progression of the disease process.

The authors conclude as follows: (1) ^{32}P is an effective agent in the treatment of chronic granulocytic and lymphocytic leukaemia and polycythaemia vera; (2) it is not of any significant benefit in Hodgkin's disease, multiple myeloma, acute leukaemia, or mycosis fungoides; (3) patients treated with ^{32}P survive approximately as long as those treated by other methods; and (4) other forms of treatment—irradiation, venesection, blood transfusion, and administration of antibiotics and steroids—may be required in addition in individual cases.

Norman Mackay

1509. **Topical Beta Ray Therapy for Superficial Skin Carcinomata and Keratoses**

M. ROTH and J. N. CASTLE. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **79**, 927–960, June, 1958. 22 figs., 15 refs.

An improved technique for the application of blotting paper impregnated with radioactive phosphorus (^{32}P) to superficial carcinomatous skin lesions (thickness less than 1 mm.) is described in this paper from the Veterans Administration Hospital and University of California Medical Center, San Francisco. For small lesions the blotting paper, cut to size, is immersed by its edge in just that quantity of a solution of ^{32}P which it will absorb; it is then dried, autoradiographed, and taped to the skin. For larger lesions the quantity of ^{32}P solution which will saturate a 7·5 cm. square of paper (2·9 ml. per 58 sq. cm. in the authors' series) is placed in a dish of the same size. A small quantity of dibasic sodium phosphate as a carrier and a wetting agent are added. The paper is immersed, dried, autoradiographed, and then backed with a piece of lead foil on which the lesion pattern has already been traced. The pattern is then cut out and applied to the lesion with tape. These methods achieve a more uniform distribution of activity as judged by autoradiography, and the method adopted for larger lesions reduces the exposure hazard to the technician.

The dose of ^{32}P is 4,000 μc. per hour per sq. cm. with an air-backed dressing and 2,500 μc. per hour per sq. cm. with a lead-backed dressing (the latter allowing for a 60% increase from back scatter off the lead). Depending on the available concentration of ^{32}P, the treatment time varied from 11 to 49 hours; this did not appear to affect the reaction, which also appeared to be independent of the area treated, with the exception that with an area of 20 sq. cm. the peak reaction was perhaps increased.

Erythema was usually present when the dressing was removed, rising to a peak during the third week, healing being complete by the ninth week. The skin in 60% of cases showed " pink atrophy " initially; in the remaining cases the lesions healed with normal skin. After 6 months most lesions showed some degree of depigmentation and white atrophy. Telangiectases were noted in a few cases. Six cases of multiple lesions are described in detail.

In an addendum the authors recommend that a very thin unit density film should be placed between the blotting paper and the skin to avoid contamination of the skin with ^{32}P. *J. G. Stewart*

SUBJECT INDEX TO VOLUME 24

JULY—DECEMBER, 1958

References are to page numbers. An asterisk denotes title and reference only

AUTHOR INDEX TO VOLUME 24

JULY—DECEMBER, 1958

References are to page numbers. An asterisk denotes title and reference only

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